

Palladium-Catalyzed Homocoupling Reaction of 1-Iodoalkynes: A Simple and Efficient Synthesis of Symmetrical 1,3-Diynes

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Abstract: This paper describes a highly efficient synthetic method of symmetrical 1,3-diynes from 1-iodoalkynes in the presence of 4 mol % Pd(PPh₃)₄ in DMF at room temperature under a nitrogen atmosphere without any use of additives and other metals.

Diyne compounds are of paramount importance as versatile building blocks,¹ among which 1,3-diynes have been prominently utilized as equivalents to various functional groups in organic synthesis² as well as valuable intermediates for natural products³ and pharmaceuticals, particularly antifungal agents.⁴ Especially noteworthy is that 1,3-diynes have been recently recognized as a core functional group in organic molecular materials such as molecular wires and molecular architecture on the nanometer scale.⁵ In connection with our current research interest in the synthetic utility of organoindium,⁶ we had previously reported on Pd-catalyzed cross-coupling reactions of allylindiums or allenylindiums with a variety of

electrophilic cross-coupling partners.⁷ On the basis of these results, we investigated intensively cross-coupling reactions of 1-iodoalkyne with organoindium reagents to form sp³–sp³ C–C bonds but could obtain only the unexpected 1,3-diynes, which are homocoupling products instead of cross-coupling products. Although transition metal-catalyzed cross-coupling reaction by use of a variety of nucleophilic coupling partners (B, Zn, Mg, Li, Cu, Al, Zr, Si) provides a very efficient method for the construction of C–C bonds,⁸ the construction of sp–sp C–C bonds has received relatively little attention. The Hay modification of the Glaser reaction is the most commonly used synthetic methodology for the synthesis of diynes.² Rossi reported that 1-alkynes were converted to 1,3-diynes with Pd(PPh₃)₄, CuI, and Et₃N in benzene in the presence of chloroacetone.^{2c} Although arylacetylenes gave good to excellent yields of diaryldiynes under these conditions, aliphatic 1-alkynes afforded mixtures of 1,4-dialkyl-1,3-butadiynes (30–50%) and 3-alkyl-4-(1-alkynyl)hexa-1,5-diyne-3-enes (38–50%). Burton developed a facile synthesis of both aromatic and aliphatic 1,3-diynes using an excess of diisopropylamine as a solvent and base.^{2f} More recently, the synthesis of diynes has been accomplished using a copper-mediated cross-coupling reaction of a variety of electrophilic coupling partners with copper(I) acetylides.⁹ Herein, we report a highly efficient synthetic method of symmetrical 1,3-diynes from 1-iodoalkynes in the presence of Pd(0) catalyst without any use of copper salts or other metal reagents and a base (Scheme 1).

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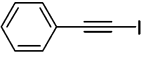
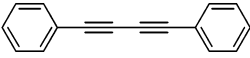
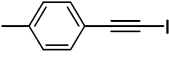
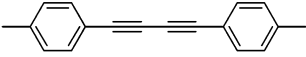
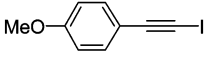
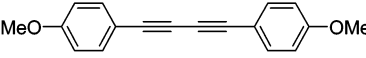
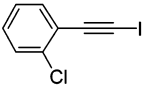
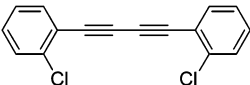
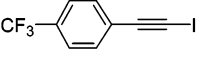
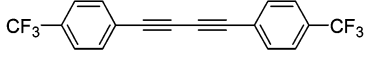
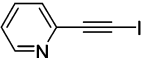
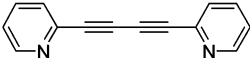
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TABLE 1. Preparation of Symmetrical 1,3-Diynes from 1-Iodoalkynes by Use of Pd(0) Catalyst^a

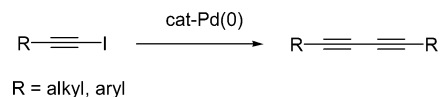
Entry	Substrate	Product	Time (h)	Yield ^b (%)
1	$n\text{-C}_5\text{H}_{11}\text{-C}\equiv\text{C-I}$	$n\text{-C}_5\text{H}_{11}\text{-C}\equiv\text{C-C}\equiv\text{C-n-C}_5\text{H}_{11}$	4	84
2	$n\text{-C}_6\text{H}_{13}\text{-C}\equiv\text{C-I}$	$n\text{-C}_6\text{H}_{13}\text{-C}\equiv\text{C-C}\equiv\text{C-n-C}_6\text{H}_{13}$	2.5	80
3			2	95
4			3	93
5			3	95
6			5	70
7			5	82
8			3	75

^a All reactions were performed using 1 mmol of 1-iodoalkyne and 4 mol % Pd(PPh₃)₄ in DMF (2 mL). The reactions were performed at room temperature, and the progress of the reactions was monitored by TLC. ^b Isolated yields were reported.

The catalytic activity of several palladium complexes was initially examined in homocoupling reaction of 1-iodophenylacetylene. Of the catalytic systems screened, the best results were obtained with 4 mol % Pd(PPh₃)₄ in DMF at room temperature for 2 h under a nitrogen atmosphere, and 1,4-diphenylbutadiyne was produced in 95% yield. DMF was the solvent of choice among several reaction media screened. 1-Iodophenylacetylene was prepared from the reaction of phenylacetylene with ethylmagnesium bromide, followed by treatment of iodine.¹⁰

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of 1-iodoalkynes to obtain 1,3-diynes in good yields under optimum conditions (Table 1). Treatment of 1-iodooctyne with 4 mol % Pd(PPh₃)₄ afforded 7,9-hexadecadiyne in 80% yield, which is a homocoupling product (entry 2). For a vast number of derivatives of phenylethynyl iodide, the presence of various substituents, e.g., 4-methyl (entry 4), 4-methoxy (entry 5), 2-chloro (entry 6), and 4-trifluoromethyl (entry 7), on the aromatic ring did not diminish the efficiency. Subjecting 4-iodoethynylmethylbenzene to Pd(0) catalyst produced 1,4-bis(4-methylphenyl) butadiyne 93% yield (entry 4). The yield of the homocoupling product was increased for iodophenylacetylene derivatives possessing an electron-donating substituent such as methoxy group (entry 5). Homocoupling reaction of iodophenylacetylene possessing trifluoromethyl as an electron-withdrawing substituent in the presence of Pd(0) catalyst produced the desired product in 82% yield (entry 7). These results contrast the fact that an electron-

SCHEME 1

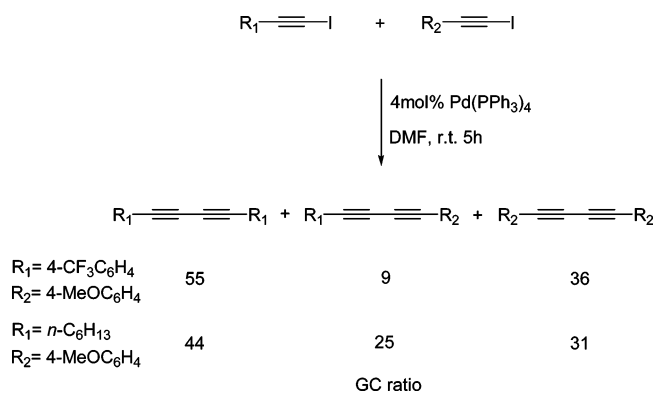


withdrawing group on aryl halides generally enhances the rate of oxidative addition of this substrate to the palladium center.⁷ Homocoupling reaction of 2-iodoethynylpyridine possessing a nitrogen atom gave the corresponding 1,3-diyne in 75% yield (entry 8). With regard to the potential utility of unsymmetrical 1,3-diynes in synthetic chemistry, unsymmetrical 1,3-diynes possessing an electron-donating group and an electron-withdrawing group are compounds of high interest because they can be used in material sciences. Therefore, we turned our attention to the preparation of unsymmetrical 1,3-diynes. Reaction of 4-trifluoromethylphenylacetylene with 4-methoxyphenylacetylene yielded mixtures of homo and hetero cross-coupling products. Mixtures of 1,3-diynes were similarly obtained in the case of cross-coupling reaction of aromatic 1-iodoalkyne with aliphatic 1-iodoalkyne under optimum conditions (Scheme 2).

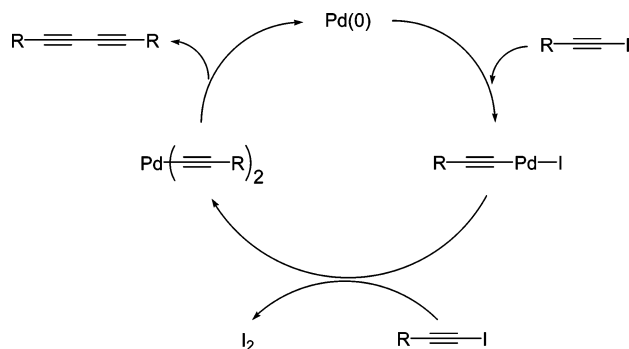
Although the mechanism of homocoupling reaction of 1-iodoalkyne is not clear at the moment, we assume that oxidative addition product of the Pd(0) species to 1-iodoalkyne reacts with other 1-iodoalkyne to produce the 1,3-diynes and iodine via the formation of dialkynylpalladium intermediate followed by reductive elimination (Scheme 3). Because 1,2-diiodostyrene was produced in major compound in the absence of Pd(PPh₃)₂Cl₂ or CuI when terminal alkynes underwent self-coupling reactions under Burton's conditions,²¹ that is to say 1-iodoalkyne

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SCHEME 2



SCHEME 3



was not an intermediate in this reaction, the mechanism of the present reaction is clearly different from Burton's. The elucidation of detailed reaction mechanism must await further study.

In conclusion, we have successfully developed a novel synthetic method of symmetrical 1,3-diynes from 1-iodoalkynes in the presence of Pd(0) catalyst without any use of copper salts or other metal reagents and a base. Because the present reaction can be carried out under an inert atmosphere, side reactions associated with the Glaser coupling reaction, which uses O_2 as the oxidant, can be avoided. Although the alkynyl derivatives need first to be transformed into the iodo derivatives, the absence of a need for CuI and base can make the presented method interesting and valuable.

Experimental Section

General Experimental Procedure. To Pd(PPh₃)₄ (0.04 mmol) was added a solution of 1-iodoalkyne (1 mmol) in dry DMF (2 mL) under a nitrogen atmosphere. After 2–5 h, the mixture was poured into an aqueous saturated NaHCO₃ solution (15 mL)

and then extracted with diethyl ether (15 mL × 3). The combined organics were washed with brine (15 mL), dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding 1,3-diyne in 70–95% yield.

Tetradeca-6,8-diyne: ¹H NMR (400 MHz, CDCl₃) δ 2.24 (t, *J* = 6.86 Hz, 4H), 1.20–1.58 (m, 12H), 0.89 (t, *J* = 6.86 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 77.92, 65.61, 31.38, 28.42, 22.55, 19.56, 14.30; IR (film) 2953, 2937, 2152, 1461, 1259, 744; HRMS (EI) calcd for C₁₄H₂₂ M⁺ 190.1721, found 190.1724.

Hexadeca-7,9-diyne: ¹H NMR (400 MHz, CDCl₃) δ 2.22 (t, *J* = 7.41 Hz, 4H), 1.16–1.62 (m, 16H), 0.86 (t, *J* = 7.41 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 77.56; 65.23, 31.30, 28.53, 28.32, 22.52, 19.22, 14.05; IR (film) 2986, 2128, 1425, 1262, 739; HRMS (EI) calcd for C₁₆H₂₆ M⁺ 218.2035, found 218.2036.

Diphenyl Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 7.50 (m, 4H), 7.30–7.40 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 132.93, 129.65, 128.88, 122.21, 82.00, 74.36; IR (film) 3049, 2978, 2145, 1261, 740; HRMS (EI) calcd for C₁₆H₁₀ M⁺ 202.0783, found 202.0780.

1,4-Bis(4-methylphenyl) Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 10.95 Hz, 4H), 7.25 (d, *J* = 10.95 Hz, 4H), 2.35 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 139.48, 132.38, 129.21, 118.77, 81.53, 73.43, 21.62; IR (film) 3056, 2991, 2131, 1268, 749; HRMS (EI) calcd for C₁₈H₁₄ M⁺ 230.1096, found 230.1093.

1,4-Bis(4-methoxyphenyl) Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 7.45 (d, *J* = 8.85 Hz, 4H), 6.85 (d, *J* = 8.85 Hz, 4H), 3.82 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.22, 134.04, 114.12, 113.92, 81.23, 72.94, 55.33; IR (film) 3058, 2982, 2142, 1262, 1025, 737; HRMS (EI) calcd for C₁₈H₁₄O₂ M⁺ 262.0994, found 262.1003.

1,4-Bis(2-chlorophenyl) Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 7.60 Hz, 2H), 7.42 (d, *J* = 7.60 Hz, 2H), 7.31 (t, *J* = 7.60 Hz, 2H), 7.24 (t, *J* = 7.60 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 137.38, 134.79, 130.70, 129.87, 126.98, 122.21, 79.82, 78.78; IR (film) 2924, 2149, 1465, 1429, 1048, 750; HRMS (EI) calcd for C₁₆H₈Cl₂ M⁺ 270.0003, found 270.0012.

1,4-Bis(4-trifluoromethylphenyl) Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 7.58–7.65 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 132.82, 131.27, 125.52, 125.49, 125.45, 80.96, 75.63; IR (film) 2959, 2918, 1607, 1315, 830; HRMS (EI) calcd for C₁₈H₈F₆ M⁺ 338.0530, found 338.0516.

1,4-Bis(2-pyridyl) Butadiyne: ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 4.59 Hz, 2H), 7.70 (t, *J* = 8.04 Hz, 2H), 7.55 (d, *J* = 8.04 Hz, 2H), 7.30 (t, *J* = 6.89 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 150.79, 142.30, 136.58, 128.80, 124.17, 81.27, 73.56; IR (film) 3048, 2981, 2155, 1461, 1421, 1268, 733; HRMS (EI) calcd for C₁₄H₈N₂ M⁺ 204.0687, found 204.0682.

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