

Gold-Catalyzed Homocoupling Reaction of Terminal Alkynes to 1,3-Diynes

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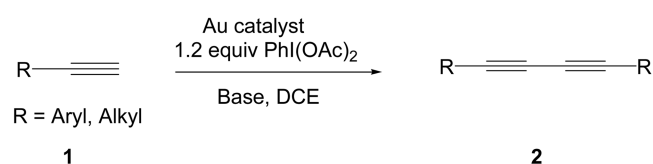
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Diyne compounds have received considerable attention in view of their applications in the field of material chemistry such as linearly π -conjugated acetylenic oligomers, polymers macrocycles and supramolecular scaffolds.¹ In addition, they are found as substructures in the formation of valuable intermediates for natural products² and pharmaceuticals such as antitumor,³ antiinflammatory⁴ and antifungal agents.⁵ As a consequence, much attention has been paid to the development of new and efficient methods for the synthesis of diynes.⁶ Traditional methods for the synthesis of 1,3-diynes include Glaser coupling,⁷ Eglinton coupling,⁸ Hay coupling,⁹ mediated by copper-catalyzed oxidative homocoupling reaction of terminal alkynes¹⁰ and Palladium-assisted Glaser-type coupling reactions.¹¹ Compared to the copper and palladium catalysis other transition-metal mediated homocoupling reactions for the synthesis of 1,3-diynes are still limited.¹²

On the other hand, gold salts and complexes have emerged as powerful catalysts for electrophilic activation of carbon-carbon multiple bonds toward a variety of nucleophiles in the past few years.¹³ The activation of alkynes or allenes with carbophilic Lewis-acidic gold salts enable the development of novel routes to complex molecular structures.¹⁴ Besides the activation of π -systems, gold can also potentially promote oxidative coupling involving gold(I)/gold(III) cycles. Recent examples were developed for the gold-catalyzed oxidative dimerization of propargylic acetates and oxidative cross-coupling reactions with preactivated arylboronic acids.¹⁵ the gold-catalyzed diamination of alkenes,¹⁶ or the oxidative coupling of nonactivated arenes.¹⁷ This gold(I)/gold(III) cycles has also been invoked in gold-catalyzed Suzuki reactions using soluble gold catalysts at rather high reaction temperatures.¹⁸ Previously, Corma and co-workers reported the gold-catalyzed Sonogashira reactions *via* a gold(I)/gold(III) catalytic cycle. In these reactions, however, common side products, 1,3-diynes, were

**Scheme 1.** Gold-catalyzed homocoupling reaction of terminal alkynes.

formed in low yields.¹⁹ As a continuation of our interest in the design and discovery of new reactions catalyzed by gold salts,²⁰ herein, we report a new protocol for the synthesis of 1,3-diyne systems by the gold-catalyzed homocoupling reaction of terminal alkynes in the presence of iodosobenzene diacetate [PhI(OAc)₂] under mild conditions (Scheme 1).

Results and Discussion


Our initial investigation focused on the reaction of phenylacetylene as an example for the optimization of the reaction conditions. We found that treatment **1a** with PPh₃AuCl (5 mol %), PhI(OAc)₂ (1.2 equiv) and Na₂CO₃ (1.5 equiv) in 1,2-dichloroethane at 60 °C afforded the desired product **2a** in 82% yield after 6 h (Table 1, entry 1). With this encouraging result, we first examined the influence of the gold source on the reaction. Cationic gold complexes such as Ph₃PAuOTf, Ph₃PAuNTf₂ and Ph₃PAuOAc afforded **2a** in 70%, 74% and 85% yield, respectively. Gold complex bearing a NHC ligand was less efficient (Table 1, entries 2-5).

Table 1. Optimization for the Au-Catalyzed homocoupling reaction of **1a**^a

Entry	Au catalyst (5 mol %)	Solvent	Base	Yield (%) ^b
1	PPh ₃ AuCl	1,2-DCE	Na ₂ CO ₃	82
2	Ph ₃ PAuOTf	1,2-DCE	Na ₂ CO ₃	70
3	Ph ₃ PAuNTf ₂	1,2-DCE	Na ₂ CO ₃	74
4	Ph ₃ PAuOAc	1,2-DCE	Na ₂ CO ₃	85
5	(NHC)AuCl	1,2-DCE	Na ₂ CO ₃	56
6	PPh ₃ AuCl	CH ₃ CN	Na ₂ CO ₃	80
7	PPh ₃ AuCl	THF	Na ₂ CO ₃	78
8	PPh ₃ AuCl	MeC ₆ H ₅	Na ₂ CO ₃	72
9	PPh ₃ AuCl	1,2-DCE	NaOAc	87
10	PPh ₃ AuCl	1,2-DCE	K ₂ CO ₃	91
11	PPh ₃ AuCl	1,2-DCE	Et ₃ N	c
12	PPh ₃ AuCl	1,2-DCE	<i>i</i> -Pr ₂ NH	c

^aReactions were carried out using **1a** (0.5 mmol), Au catalyst (5 mol %), PhI(OAc)₂ (1.2 equiv) and base (1.5 equiv) in 5 mL of solvent at 60 °C under N₂ atmosphere for 6 h. ^bIsolated yields. ^cNo product was obtained.

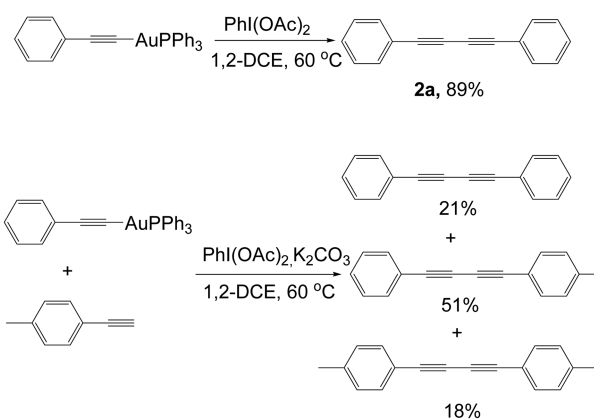
Table 2. Gold-catalyzed homocoupling reactions of alkynes^a

Entry	R	Time (h)	Yield (%) ^b
1	C ₆ H ₅ -	6	2a , 91
2	4-Me-C ₆ H ₄ -	6	2b , 90
3	2-Me-C ₆ H ₄ -	8	2c , 84
4	2-Cl-C ₆ H ₄ -	6	2d , 88
5	4-F-C ₆ H ₄ -	4	2e , 85
6	4-CF ₃ -C ₆ H ₄ -	4	2f , 90
7	4-MeO-C ₆ H ₄ -	10	2g , 73
8	<i>n</i> -C ₄ H ₉ -	10	2h , 70
9	<i>n</i> -C ₅ H ₁₁ -	10	2i , 75
10	<i>n</i> -C ₆ H ₁₃ -	10	2j , 72
11	<i>t</i> -Bu-	10	2k , 80
12		10	2l , 80
13	AcOCH ₂ -	10	2m , 67

^aReactions were carried out using **1** (0.5 mmol), Ph₃PAuCl (5 mol %), PhI(OAc)₂ (1.2 equiv) and base (1.5 equiv) in DCE (5 mL) at 60 °C under N₂ atmosphere. ^bIsolated yield.

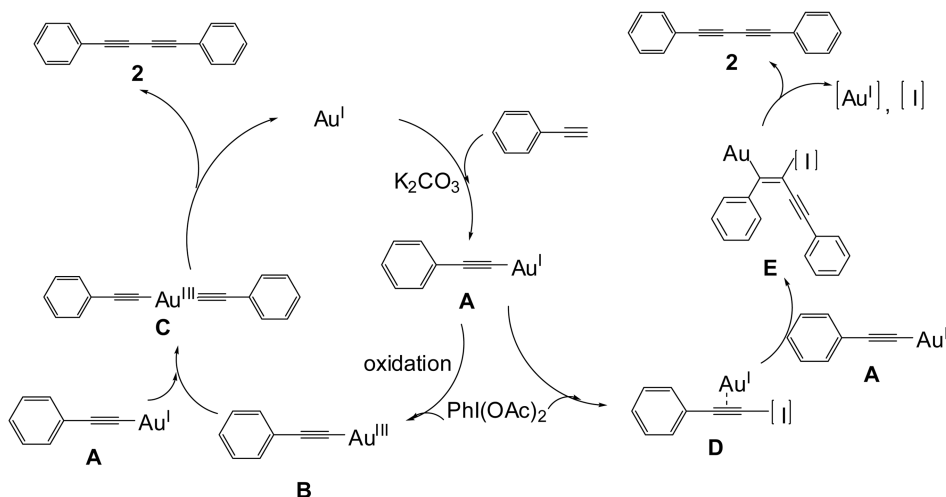
Next, a series of solvents were examined for the homocoupling reaction of phenylacetylene. Using acetonitrile as the solvent, the desired 1,3-diyne **2a** was obtained in 80% yield (Table 1, entry 6). On using other solvent such as THF or toluene, the desired product **2a** could be isolated in low yields (Table 1, entries 7 and 8). Addition of different bases was also examined. NaOAc and K₂CO₃ showed moderate improvement (Table 1, entries 9 and 10), whereas K₂CO₃ afforded **2a** in an optimized 91% yield. Other bases such as diisopropylamine, Et₃N were turned out to be totally disfavored (Table 1, entries 11 and 12).

With the optimal reaction conditions in hand, we proceeded to extend the scope of the reaction, and the results are summarized in Table 2. The results show that both aromatic and aliphatic terminal alkynes successfully underwent the

**Scheme 2.** The cross-coupling of [(PPh₃)Au(phenylethynyl)] with alkyne.

homocoupling to produce the corresponding 1,3-diyne in moderate to high yields. For substituted phenylacetylenes bearing methyl group or halogen substituents, the homocoupling all worked well with 5 mol % PPh₃AuCl catalyst, even for the substrates bearing strong electron-withdrawing trifluoromethyl group (Table 2, entries 2-6), whereas the electron-donating methoxy group was present, the reaction took a longer time and the yield was only 73% (Table 2, entry 7). The diminished yield in this case was due to the weaker acidity of the acetylenic proton. When aliphatic alkynes were used, the yields were somewhat lower (Table 2, entries 8-11) compared with aromatic alkynes and the homocoupling needed to prolong the reaction time. The PPh₃AuCl catalyzed homocoupling of alkynes bearing different functional groups such as 1-ethynyl cyclohexene and propargyl acetate, was also carried out smoothly to afford the corresponding 1,3-diyne **2l-m** in 80% and 67% yields, respectively (Table 2, entries 12, 13).

To understand the reaction mechanism for the formation of 1,3-diyne, we conducted the reaction of [(PPh₃)Au(phenylethynyl)] with PhI(OAc)₂ (1.2 equiv) in 1,2-dichloroethane at 60 °C. As a consequence, the desired

**Scheme 3.** Possible reaction mechanism.

product **2a** was obtained in 89% yield. This indicates that [(PPh₃)Au(phenylethynyl)] plays a key role in the reaction mechanism. Additionally, an attempt at cross-coupling reaction of [(PPh₃)Au(phenylethynyl)] with 4-methylphenylacetylene was investigated briefly and resulted in a statistical distribution of diynes along with the cross-coupled products (Scheme 2).

Based on the above results and related literature,²¹ a plausible reaction mechanism is depicted in Scheme 3. The reaction of Ph₃PAuCl with the corresponding acetylene would form alkynylgold(I) **A** in the presence of base, which is then oxidized by iodosobenzene diacetate to give a Au(III) species **B**. The transmetalation from **A** to **B** could lead to the diorganogold (III) intermediate **C**, which could then undergo reductive elimination to give 1,3-diyne **2** and regenerate the gold(I) catalyst. Alternatively, the reaction may involve the intermediate alkynyl-iodonium complex **D**, which is formed by the reaction of alkynylgold(I) **A** with PhI(OAc)₂. The alkynyl-iodonium **D** undergoes the subsequent addition with alkynylgold(I) **A** to afford a vinylgold intermediate **E** followed by β-elimination to regenerate the Au(I) catalyst and afford the final product **2**.

Conclusion

In conclusion, we have developed a mild and efficient protocol for gold-catalyzed oxidative homocoupling of various terminal alkynes. In the presence of Ph₃PAuCl, a variety of terminal alkynes underwent oxidative homocoupling afford the corresponding symmetrical 1,3-diynes in moderate to good yields. The application of this powerful strategy in organic synthesis and more detailed mechanistic investigations are currently underway in our laboratory.

Experimental Section

General Procedure for Ph₃PAuCl-catalyzed Oxidative Homocoupling of Terminal Alkynes. The mixture of phenylacetylene (**1a**, 0.5 mmol), Ph₃PAuCl (5 mol %), PhI(OAc)₂ (1.2 equiv) and K₂CO₃ (1.5 equiv) in DCE (5 mL) was stirred at 60 °C in a 25 mL two-necked round-bottom flask under N₂ atmosphere. Until the reaction completed, the solvent was removed and the crude product was separated by column chromatography to give the pure samples of symmetrical diynes **2a**. ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.54 (m, 4H), 7.30–7.35 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 132.6, 129.3, 128.5, 122.1, 81.8, 75.2. MS (EI) *m/z*: 202, 174, 126, 101, 88.

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