

Gold-catalyzed efficient tandem assembly of terminal alkynes and arynes: synthesis of alkynylated biphenyl derivatives†

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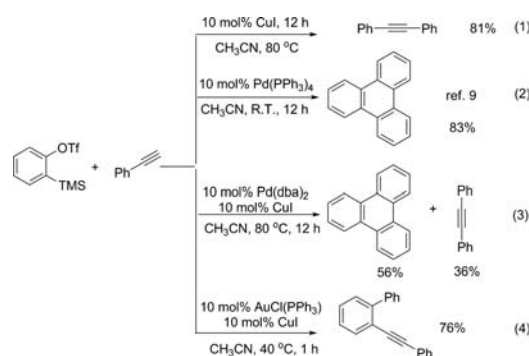
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Gold catalysts have been found to catalyze the tandem assembly of arynes and terminal alkynes efficiently in the presence of CuI under mild reaction conditions to provide useful alkynylated biphenyl derivatives.

During the past few years, gold has emerged as one of the most efficient catalysts for the creation of carbon–carbon and carbon–heteroatom bonds under mild conditions.¹ Besides its unique properties in hydrogenation and selective oxidation,² gold is found to be an extraordinary catalyst for the activation of alkynes, allenes, and alkenes.³ The subsequent inter- or intramolecular addition of nucleophiles such as alkenyl, oxygen-, and nitrogen-containing functionalities, has created many novel catalytic possibilities and allowed the development of useful and selective reactions.⁴ Arynes are very active π -components, but their uses in transition metal-catalyzed organic syntheses are partially limited by the harsh preparation conditions and uncontrolled reactivity, although stoichiometric reactions of zirconium–benzyne and nickel–benzyne complexes were studied.⁵ Recently, a mild method for the preparation of arynes *in situ* at moderate temperatures from commercially available *o*-silyl aryl triflates⁶ promoted the exploration of the reactions using arynes as the substrates⁷ and the transition metal-catalyzed reaction sequences indeed occurred with arynes in high efficiency.⁸ The palladium-catalyzed cyclotrimerization⁹ of arynes, cocyclotrimerization of arynes with alkynes,¹⁰ arynes with allylic halides,¹¹ arynes with aryl halides,¹² aryne with benzyl bromide,¹³ and so on,¹⁴ have been reported. However, the high propensity of arynes to cyclotrimerize in the presence of palladium is problematic in some cases, and the gold catalyzed reactions involving arynes are extremely rare.¹⁵ Our ongoing research program on employing arynes as useful substrates in organic synthesis¹⁶ prompted us to explore the function of gold in the reaction of arynes. Herein we report the unique catalytic properties of gold in the reaction of terminal alkynes and arynes.

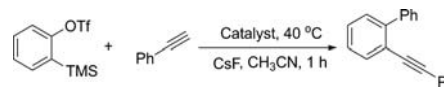
Alkynes have attracted much attention and great effort has been put into their inter- and intramolecular carbometalation reactions.¹⁷ In our initial research, we examined the reaction of benzyne with 1-ethynylbenzene in the presence of various metal catalysts. The nature of the catalysts significantly affects the selectivity of the reaction as shown in Scheme 1. For example, the use of 10 mol% CuI favored the formation of 1,2-diphenyl-



Scheme 1 Diverse properties of metal catalysts.

ethyne (eqn (1)), which was isolated in 81% yield, while the use of Pd(PPh₃)₄ led to the cyclotrimerization of benzyne with the triphenylene as the major product (eqn (2)). The combination of 10 mol% Pd(dba)₂ and 10 mol% CuI, which is a typical catalyst for the Sonogashira reaction, showed poor selectivity, and triphenylene (56%) and 1,2-diphenylethyne (36%) were isolated (eqn (3)). It should be noted that 10 mol% AuClPPh₃ and 10 mol% CuI led to a different tandem assembly compared to that found with the other metals examined, and the alkynylated biphenyl derivative, which is particularly useful in the synthesis of polycyclic aromatic systems,¹⁸ was obtained in good yield under mild conditions (eqn (4)). A trace of diphenyl acetylene was detected by GC-MS analysis, but it was easily separated from the biphenyl derivative. This result represents the first example of a selective gold-catalyzed reaction involving aryne and terminal alkyne.

Table 1 Screen of reaction conditions^a

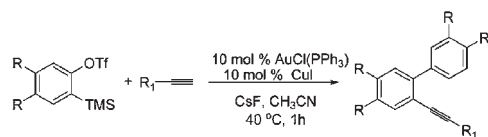


Entry	Catalyst	Yield (%) ^b
1	NaAuCl ₄ (10 mol%) or AuClPPh ₃ (10 mol%)	Trace
2	NaAuCl ₄ (10 mol%) + AgSbF ₆ (10 mol%)	37
3	NaAuCl ₄ (10 mol%) + CuI (10 mol%)	56
4	NaAuCl ₄ (10 mol%) + AgOTf (10 mol%)	32
5	AuClPPh ₃ (10 mol%) + CuI (10 mol%)	71
6	AuClPPh ₃ (10 mol%) + CuCl (10 mol%)	70
7	CuI (10 mol%) + PPh ₃ (10 mol%)	17 (76)
8	CuCl (10 mol%) + PPh ₃ (10 mol%)	14 (72)
9	CuCl ₂ (10 mol%) + PPh ₃ (10 mol%)	16 (58)

^a Reaction conditions: 2-(trimethylsilyl)phenyl triflate (180 mg, 0.6 mmol), phenylacetylene (31 mg, 0.3 mmol), CsF (276 mg, 1.8 mmol), gold catalyst (0.03 mmol), co-catalyst (0.03 mmol), CH₃CN (5 mL), 40 °C (bath temp.), 1 h. ^b Isolated yields. 1,2-Diphenylethyne was isolated as the main product as shown in parentheses in entries 7–9.

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data (¹H NMR, ¹³C NMR and HRMS) for the products. See DOI: 10.1039/b806821f

Table 2 Gold-catalyzed coupling reaction of terminal alkyne and arynes^a

Entry	R	Alkyne	Product	Yield (%) ^b	Entry	R	Alkyne	Product	Yield (%) ^b
1	H	$\equiv\text{-C}_4\text{H}_9\text{-}n$		88	10	Me	$\equiv\text{-Ph}$		66
2	H	$\equiv\text{-C}_6\text{H}_{13}\text{-}n$		73	11	Me	$\equiv\text{-Ph}$		68
3	H	$\equiv\text{-Ph}$		71	12	Me	$\equiv\text{-Ph-Et}$		74
4	H	$\equiv\text{-Ph}$		74	13	Me	$\equiv\text{-Ph-F}$		77
5	H	$\equiv\text{-Ph-Et}$		75	14	-OCH ₂ O-	$\equiv\text{-Ph}$		85
6	H	$\equiv\text{-Ph-OMe}$		70	15	H	$\equiv\text{-C}_6\text{H}_{11}$		61
7	H	$\equiv\text{-Ph-F}$		89	16	Me	$\equiv\text{-C}_6\text{H}_{11}$		60
8	Me	$\equiv\text{-C}_4\text{H}_9\text{-}n$		65	17	H	$\equiv\text{-N}$		57
9	Me	$\equiv\text{-C}_6\text{H}_{13}\text{-}n$		67	18	H	$\equiv\text{-CH}_2\text{OH}$		52

^a Reaction conditions: benzyne precursors (0.6 mmol); 1-ethynyl-benzene (31 mg, 0.3 mmol); CsF (276 mg, 1.8 mmol); AuClPPh₃ (15 mg, 0.03 mmol); CuI (6 mg, 0.03 mmol), CH₃CN (5 mL); 40 °C (bath temp.); 1 h. ^b Isolated yields.

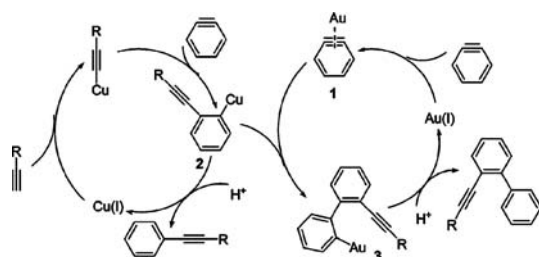
An attempted reaction using NaAuCl₄ (10 mol%) or AuClPPh₃ (10 mol%) alone without the co-catalyst did not work (Table 1, entry 1). The replacement of CuI with AgSbF₆ or AgOTf led to a decrease of the yields (Table 1, entries 2–4). The

best result was presented by combination of AuClPPh₃ (10 mol%) and CuI (10 mol%), and the mixture of AuClPPh₃ (10 mol%) and CuCl (10 mol%) also afforded a comparable yield (Table 1, entries 5–6).

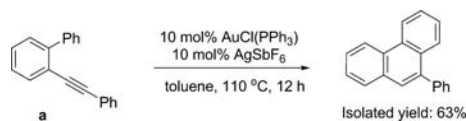
The gold catalyst system was then applied to various terminal alkynes and arynes, and the results are summarized in Table 2. A range of alkyl-substituted alkynes afforded the desired biphenyl derivatives in good yields (Table 2, entries 1–2, 8–9). Aryl substituents were well tolerated with electron-donating and fluoride-substituted aryl alkynes (Table 2, entries 3–7). The coupling reaction also demonstrated a tolerance toward a variety of arynes (Table 2, entries 8–14). Notably, the conjugated enyne smoothly underwent the selective reaction and afforded the biphenyl compounds containing 1,4-enyne (Table 2, entries 15–16). The 2-ethynylpyridine was also found to be a viable substrate for the gold-catalyzed aryne reaction (Table 2, entry 17). Moreover, terminal alkyne bearing activated hydrogen like prop-2-yn-1-ol has been found to be a reliable reaction partner and a moderate yield can be obtained (Table 2, entry 18). The reaction of 4-methylbenzynes and 4-fluorobenzynes gave a mixture of regioisomers.

In order to study the role of gold, we performed the reaction in the absence of gold catalyst (Table 1, entries 7–9). Given the presence of triphenylphosphine, 1,2-diphenylethyne was isolated in moderate to good yields with CuI, CuCl, or CuCl₂ as the catalyst, showing the crucial effect of the gold catalyst on the reaction. Based on these results, a plausible mechanism was proposed as shown in Scheme 2. First, the gold catalyst interacts with benzyne to form the intermediate **1**. Subsequent nucleophilic addition of organocopper intermediate **2** generated *in situ* from benzyne and copper acetylide forms the organogold intermediate **3**, which liberates the addition product biphenyl derivative and the gold catalyst by protodemetalation. In the absence of gold catalyst, the organocopper intermediate **2** undergoes protonolysis and provides internal alkynes. It has to be noted that the protonolysis of the organocopper intermediate **2** was fully suppressed in the presence of gold catalyst, presumably due to the rapid ensuing transformations. The products formed were not found when the reaction temperature was increased to 90 °C.

The intramolecular hydroarylation of as-prepared alkynylated biphenyl derivatives was tested, which is particularly useful in the synthesis of polycyclic aromatic systems.¹⁸ One example is the cyclization of **a** catalyzed by 10 mol% AuCl(PPh₃) and 10 mol% AgSbF₆ to form 9-phenylphenanthrene in a moderate yield of 63% (Scheme 3). Reactions of this type have been used in the synthesis of several natural products.¹⁹



Scheme 2 The possible mechanism.



Scheme 3

In conclusion, the gold catalysts have been proven to be unique catalysts for the tandem assembly of terminal alkynes and arynes, which leads to a facile and efficient method for the preparation of useful alkynylated biphenyl derivatives under mild conditions. Further studies for elucidating the reaction mechanism and extending the substrates are ongoing.

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