



On the catalytic duo PdCl₂(PPh₃)₂/AuCl(PPh₃) that cannot effect a Sonogashira-type reaction: a correction

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ABSTRACT

In contrast to the observation made by the Laguna group, we report that the combination of PdCl₂(PPh₃)₂ and AuCl(PPh₃) makes a unique catalytic system that allows Sonogashira-type cross-coupling of both aryl and alkyl alkynes with aryl halides in excellent yields.

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Among all the carbon–carbon bond forming reactions now in use, the Sonogashira reaction undeniably occupies the numero uno position in terms of its efficiency for accessing aryl alkynes and conjugated enynes, which are prevalent intermediates for the synthesis of a diverse array of natural products, pharmaceuticals, and molecular organic materials.¹ The traditional experimental procedure involves PdCl₂(PPh₃)₂ as a Pd(0) precursor and CuI as a co-catalyst in a solution containing amine bases.² The CuI is required to activate the alkynes as π -acid. Over the years, some alternatives to the CuI co-catalyst have been developed in order to overcome the problems emanating from competitive homocoupling to the diyne. These include employing stoichiometric amounts of silver oxide or tetrabutylammonium salts³ as activators or use of palladium-only procedures.⁴ Clearly, the development of a new co-catalyst other than CuI which will not allow homocoupling as a side reaction is desirable.

During the last decade or so, cationic phosphine–gold(I) complexes have found extensive use as versatile and selective catalysts for a growing number of synthetic transformations.^{5,6} The alkynophilicity of cationic Au(I) species is superior to that of other coinage metals, for example, Cu and Ag. It is conceivable that replacement of Cu(I) co-catalyst by cationic gold(I) would not only promote the Sonogashira-type cross-coupling of aryl halides with alkynes but due to extreme resistance of gold compounds to oxidation, these reactions are unlikely to be accompanied by the usual Hay/Glaser type products which are frequently observed in copper co-catalytic processes. Indeed, very recently Laguna and co-workers⁷ have demonstrated that the catalytic systems PdCl₂(PPh₃)₂/Na(AuCl₄) and PdCl₂(PPh₃)₂/AuCl(tht) (tht = tetrahydrothiophene) can give good results (~95%) for electron-deficient aryl iodides (two examples) and aryl bromides (two examples), but for bromobenzene yields drop to 5% and 26%, respectively. Furthermore, use of a different gold co-catalyst AuCl(PPh₃) was shown to be practi-

cally ineffective (<1% conversion) even in the case of an electron-poor aryl iodide, namely 4-iodoacetophenone (Scheme 1). These authors suggest that the inactivity of AuCl(PPh₃) is due to its high stability under the experimental conditions thus making it a poor pre-catalyst, whereas AuCl(tht) displays its activity since it can easily lose tht ligand and this may lead to the formation of the active catalyst in solution.

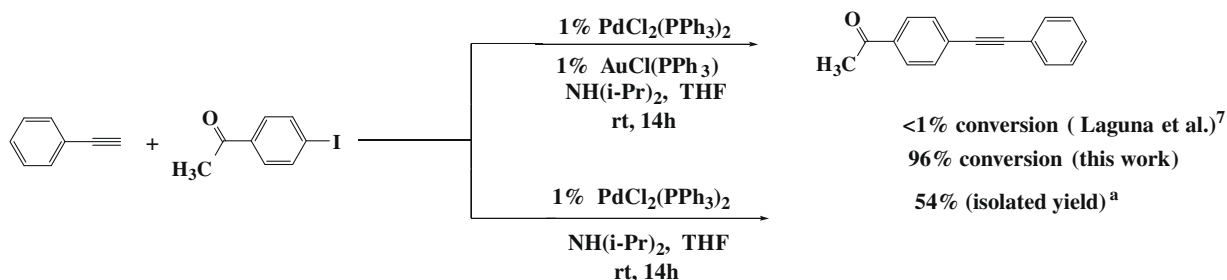
As part of a broader program on the unique reactivity of Pd–Au dual catalytic systems,⁸ we have had cause to reinvestigate the Sonogashira-type cross-coupling of 4-iodoacetophenone with phenylacetylene using a combination of PdCl₂(PPh₃)₂ and AuCl(PPh₃) under strictly Laguna and co-worker's conditions. The result was dramatic (Scheme 1): the product alkyne was obtained in excellent yield (92%) (96% conversion)!⁹ Equally surprising was the observation that omission of the co-catalyst still gives the product in 54% isolated yield. Our results are, therefore, in conflict with those reported by the Laguna group. However, it is not easy to explain the reason for this difference.

In order to probe the synthetic scope of this gold co-catalyzed Sonogashira-type reaction, it was deemed important to optimize the reaction conditions by using different bases and solvents, as well as changing the reaction temperature. We chose the cross-coupling of bromobenzene with phenylacetylene as the model reaction and the results are presented in Table 1. Clearly, the catalytic system is not powerful enough to allow the reaction in THF at ambient temperature; heating to reflux was needed in this case although prolonging the reaction time beyond 4 h did not show any effect on the yield of the reaction. The reaction also takes place in water or triethylamine, but the yields are unsatisfactory. Finally, going from THF through MeCN, DMSO, and DMF, and changing bases from Et₃N to K₂CO₃ allowed identification of PdCl₂(PPh₃)₂/AuCl(PPh₃) in DMF/DMA in the presence of Et₃N as the efficient catalytic system for the cross-coupling of bromobenzene

Under our optimized reaction conditions, we accomplished Sonogashira-type cross-coupling of a wide array of electronically and structurally diverse aryl halides (Table 2).¹⁰ With respect to

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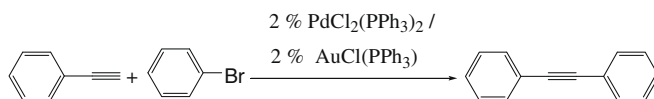
E-mail address: tksr@chem.iitkgp.ernet.in (T.K. Sarkar).



Scheme 1. ^a~7% of Hay/Glaser-type homocoupling product was also formed in this reaction.

Table 1

Effect of reaction conditions on the cross-coupling of bromobenzene with phenylacetylene^a



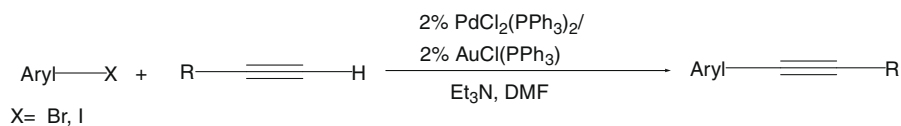
Entry	Solvent	Base	Temp (°C)	Time (h)	Yield ^b (%)
1	THF	Et ₃ N	rt	8	nr
2	THF	Et ₃ N	Reflux	4	81
3	H ₂ O	Et ₃ N	80	12	40
4	Et ₃ N	Et ₃ N	80	6	67
5	Toluene	Et ₃ N	80	6	33
6	MeCN	Et ₃ N	80	4	84
7	DMSO	Et ₃ N	80	3	89
8	DMF	Et ₃ N	80	3	96
9	DMF	K ₂ CO ₃	80	3	79
10	DMA	Et ₃ N	80	3	96

^a Reactions were run in 3 ml solvent with 1 mmol bromobenzene, 1.1 mmol phenylacetylene, and 3 mmol base.

^b Isolated yield.

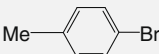
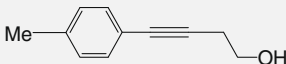
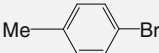
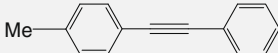
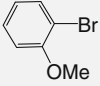
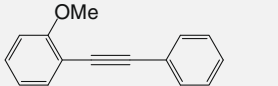
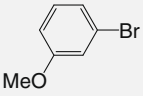
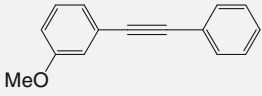
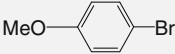
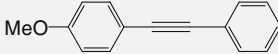
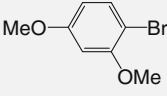
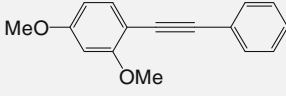
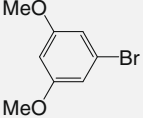
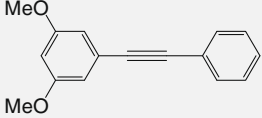
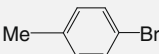
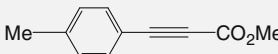
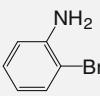
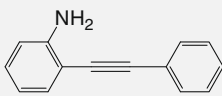
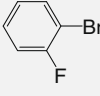
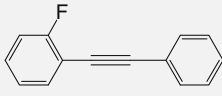
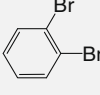
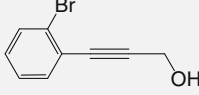
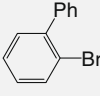
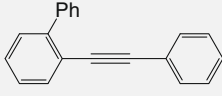
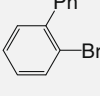
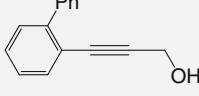
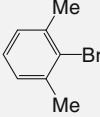
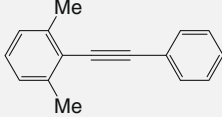
Table 2

Coupling of aryl halides with terminal alkynes



Entry	ArX	Products	Temp (°C)	Time (h)	Yield ^{a,b} (%)
1			60	0.75	93
2			70	0.5	98
3			70	0.75	92
4			80	1	98
5			80	3	91
6			80	3	96

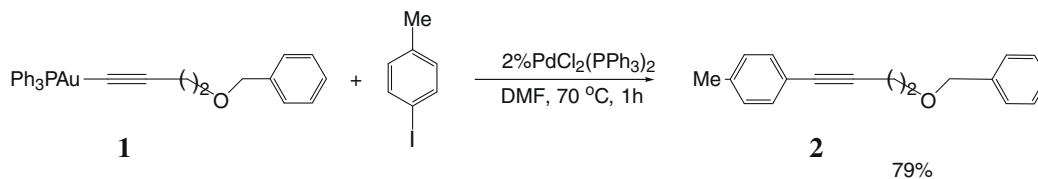
Table 2 (continued)

Entry	ArX	Products	Temp (°C)	Time (h)	Yield ^{a,b} (%)
7			80	3	91
8			80	3	94
9			80	7	91 (42)
10			80	7	93
11			80	7	94
12			90	9	90(27)
13			90	9	93(29)
14			80	5	70 ^{c,d}
15			80	4	62
16			80	3	92 ^{e,f}
17			80	3	91
18			80	4	91
19			80	4	89
20			90	6	86

^a Isolated yield.^b Yields in parentheses refer to those using CuI in place of AuCl(PPh₃).^c Cs₂CO₃ was used instead of Et₃N.^d 60% of the coupled product was isolated when K₂CO₃ was used as a base.^e Replacement of AuCl(PPh₃) by (IPr)AuCl gives the product in 94% yield in 1.5 h.^f 1% PdCl₂(PPh₃)₂/1% AuCl(PPh₃) and a reaction time of 5 h gave the product in 89% yield.

the aryl bromides¹¹ and iodides,¹² both electron-neutral and electron-poor species react with alkynes to provide the products in

excellent yields (Table 2, entries 1, 2, 5, and 6). Electron-rich aryl halides (Table 2, entries 3, 7, and 8) are amenable to this protocol;



Scheme 2.

however, more remarkable is that even extremely electron-rich systems (Table 2, 9–13) couple efficiently with alkynes. This method is also tolerant of ortho-substitution in aryl bromides (Table 2, entries 16–19). Even the highly sterically hindered aryl halides (Table 2, entries 4 and 20) couple with alkynes without any difficulties. Notably, amino groups are tolerated under these conditions as shown by the reaction of 2-bromoaniline, which is converted into the corresponding 2-substituted products (Table 2, entry 15). Alkynes containing an electron-withdrawing group (directly attached with the ethynyl carbon) are usually poor substrates for the coupling with aryl halides.¹³ It is gratifying to note that this catalytic system allows such a coupling with methyl propiolate, *albeit* in modest yield (Table 2, entry 14). Incidentally, for this reaction use of a carbonate base (e.g., K_2CO_3 and Cs_2CO_3) was essential since in the presence of NET_3 complete destruction of the acetylene source was observed. Interestingly, several examples (Table 2, entries 3, 5, 7, 17, and 19) where alkyl alkynes are found to couple efficiently with aryl halides are also in conflict with Laguna and co-worker's finding that the gold co-catalysts used in their work are much more efficient in activating aryl alkynes than alkyl alkynes.⁷

As previously noted by Laguna and co-workers,⁷ no traces of Hay/Glaser type homocoupling of alkynes could be observed (TLC) in any of the reactions described in Tables 1 and 2 which were essentially clean. Furthermore, independent experiments were carried out to see the role of Pd and Au separately in these reactions. While the gold complex $\text{AuCl}(\text{PPh}_3)$ was found to be totally inactive in the absence of the palladium complex $\text{PdCl}_2(\text{PPh}_3)_2$, the latter alone led to the formation of the coupled product (Table 2, entry 5) in 18% yield. The Pd–Au dual catalytic reactions are also possible with lower catalytic loadings, although longer reaction times are needed for efficient conversions. For example, in entry 16 (Table 2) with 1% $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/1\% \text{AuCl}(\text{PPh}_3)$ the product was obtained in 89% isolated yield after a reaction time of 5 h. Incidentally, the assumption made by Laguna and co-workers⁷ to explain the inactivity of $\text{AuCl}(\text{PPh}_3)$ in terms of lesser propensity for the dissociation of the phosphine ligand seems untenable in view of our observation that replacement of the phosphine ligand by strongly bonded *N*-heterocyclic carbene ligand (IPr NHC) still gives the product (Table 2, entry 16) in high yield (94%). It should be noted that the strong metal–carbenic bond of the NHC complex favors tight-binding kinetics, therefore lessening ligand dissociation.¹⁴ We have also compared the results of the Sonogashira coupling in the presence of the Pd–Au catalytic system with those obtained under classical conditions, that is, in the presence of CuI, and amine (under identical conditions as in Table 2 with the replacement of $\text{AuCl}(\text{PPh}_3)$ by CuI). In these cases (Table 2, entries 9, 12, and 13) yields as given in parentheses are woefully low, the predominant by-product being the Hay/Glaser type homocoupling product (31–44%).

On the basis of the Pd–Ag catalyzed coupling reaction reported by Pale and co-workers¹⁵ it may be assumed that gold acetylides are intermediates in our case and these organogold compounds enter into the Pd catalytic cycle. Indeed, preliminary work already favors this mechanism as we have found that the preformed gold acetylide **1** gives the coupled product **2** in 79% isolated yield unaccompanied by any Hay/Glaser type product (Scheme 2).^{16,17}

In conclusion, we have demonstrated that the reportedly inactive dual catalytic system $\text{PdCl}_2(\text{PPh}_3)_2/\text{AuCl}(\text{PPh}_3)$ allows efficient Sonogashira-type cross-coupling of aryl bromides and iodides. Further work is underway in this laboratory to investigate the full scope of this dual catalytic process involving even the challenging aryl chlorides as one of the partners and also to unveil the detailed mechanism of alkyne activation in this reaction.

Acknowledgments

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Supplementary data

General experimental procedure and full spectroscopic data for compounds **1** and **2** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.003.

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- Preparation of 1-(4-(phenylethynyl)phenyl)ethanone under strictly Laguna's condition: 7-iodoacetophenone (369 mg, 1.5 mmol), phenylacetylene (0.25 mL, 2.25 mmol), and $\text{NH}(i\text{-Pr})_2$ (0.33 mL, 2.25 mmol) were stirred in THF (3 mL) under argon. $[\text{PdCl}_2(\text{PPh}_3)_2]$ (10.5 mg, 0.015 mmol) was added and the mixture was stirred for 10 min before the addition of $[\text{AuCl}(\text{PPh}_3)]$ (7 mg, 0.015 mmol). The mixture was stirred at room temperature for 14 h, then it was diluted with diethyl ether (5 mL), and filtered through a small Celite bed. The filtrate was poured into water and the aqueous layer was extracted with diethyl ether (10 mL \times 3). The combined organic layer was dried over anhydrous Na_2SO_4 , and the solvent was evaporated under reduced pressure. The product was isolated by chromatography on a silica gel column, 304 mg (92%); also isolated was 4-iodoacetophenone, 17 mg (4%).
- General procedure for the Pd–Au dual catalytic Sonogashira-type cross-coupling. A flame-dried two-necked flask, equipped with a reflux condenser,

- gas inlet/outlet, and rubber septum, was evacuated and backfilled with argon (the cycle was performed twice) and then charged under a positive pressure of argon with aryl halides (1 mmol), DMF(3 mL), PdCl₂(PPh₃)₂ (14 mg, 0.02 mmol), base (3 mmol), followed by AuCl(PPh₃) (10 mg, 0.02 mmol) and terminal acetylenes (1.1 mmol). Then the reaction mixture was heated at mentioned temperature and time. It was diluted by diethyl ether (3 ml) and filtered through a small Celite bed. The filtrate was poured into water and the aqueous layer was extracted with diethyl ether (10 mL × 3). The combined organic layer was dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. The product was isolated by chromatography on a silica gel column.
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