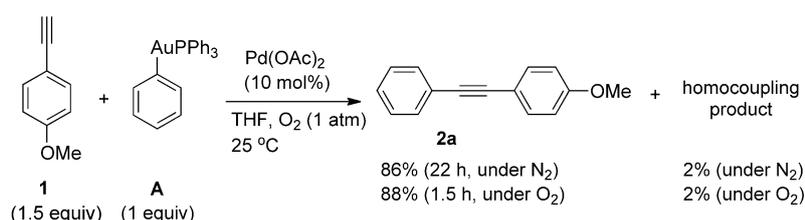


Base-Free Palladium-Catalyzed Sonogashira Coupling Using Organogold Complexes

Sreekumar Pankajakshan and Teck-Peng Loh*^[a]

Sonogashira coupling reactions^[1] boast to be one of the most elegant transition metal catalyzed protocols owing to the value of their products as important building blocks for bioactive natural products, agrochemicals, functionalized materials, and so on.^[2] The classical reaction involves a

palladium(0) catalyst with a copper co-catalyst and an amine base, which is practically often used as the solvent. Though the classical version still remains to be the popular choice, it suffers from drawbacks such as the variable reactivity of electrophilic partners (triflates > iodides > bromides > chlorides), formation of undesirable homocoupled dialkyne side products; the often need for inert conditions and higher temperatures. Much effort has been devoted in recent years to fine tune the reaction conditions and to develop facile monocatalytic systems.^[3] However, a copper-free, base-free, and ligand-free Sonogashira reaction that runs efficiently under mild aerobic conditions still remains elusive. The quest for alternatives to aryl halides is also desirable in the realm of green chemistry. To the best of our knowledge only very few aryl halide/triflate equivalents are reported to date^[4] and they all demand the necessity of a base,^[4a,c] ligand,^[4c] and/or higher temperatures.^[4a–b] Herein, we report a general palladium-catalyzed base-free aerobic Sonogashira procedure using organogold complexes at room temperature. These easily synthesized and stable complexes



Scheme 1. Model Sonogashira coupling with organogold complex **A**.

are explored for the first time^[5] in the coupling reaction with terminal alkynes.^[6–9]

The model reaction was attempted with *para*-methoxyphenylacetylene (1.5 equivalent) and (phenyl)(triphenylphosphanyl)gold^[10] (**A**, 1 equivalent) using 10 mol% of palladium acetate as the catalyst (Scheme 1). The reaction was carried out in dry degassed tetrahydrofuran under an inert atmosphere and was monitored by ³¹P NMR spectroscopy. The gold complex was consumed in 22 hours at room temperature. The Sonogashira product **2a** was isolated in 86% yield, as well as a trace amount of the homocoupling product. Curiosity over regeneration of the palladium catalyst in the catalytic cycle prompted us to try the reaction under an atmosphere of oxygen. Interestingly the presence of the oxygen accelerated the reaction multifold (completed in 1.5 h at 25 °C) and the coupling product was isolated in 88% yield (Scheme 1). It is to be noted that the presence of oxygen did not enhance the extent of homocoupling, and again only a trace of it was isolated from the reaction (Scheme 1). The reaction is equally feasible under normal air albeit with a slightly longer reaction time (6 h). Other palladium sources such as [Pd(PPh₃)₄], PdCl₂, and [PdCl₂(PPh₃)₂] were also effective in catalyzing the reaction but Pd(OAc)₂ stood out as the catalyst of choice. The palladium loading can be reduced to 3 mol% without any significant alteration in yield or reaction time but we persisted with the standard loading of 10 mol% for accurate weighing. The methodology was then extended to different alkynes (**1**) with either (phenyl)(triphenylphosphanyl)gold (**A**) or (*para*-anisyl)(triphenylphosphanyl)gold^[6a] (**B**) as the aryl source

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(Table 1). It was gratifying to find that a range of substrates can be accommodated using this coupling protocol and the reaction times were normally in the range of 1.5–2.5 hours (Table 1, entries 1–11). 1-Naphthylacetylene coupled with **B**

Table 1. Scope of different terminal alkynes for the palladium-catalyzed Sonogashira coupling with organogold complexes.

$$\text{R}-\text{C}\equiv\text{C}-\text{H} + [\text{ArAuPPH}_3] \xrightarrow[\text{THF, O}_2 (1 \text{ atm}), 25^\circ\text{C}]{\text{Pd(OAc)}_2 (10 \text{ mol}\%)} \text{R}-\text{C}\equiv\text{C}-\text{Ar}$$

Entry	Alkyne (1)	T [h]	Product (2)	Yield [%]
1		2		69
2		1.5		85
3		2		86
4 ^[a]		1.5		78
5		2		72
6		1.5		85
7		2		67
8		1.5		69
9 ^[a]		1.5		98
10		2		53
11		2		61

[a] The yield calculated from ¹H NMR spectra as the coupling product and the homo-coupled product were inseparable by column chromatography.

in 69% yield (Table 1, entry 1). *para*-Bromophenylacetylene with two potential coupling sites selectively underwent the reaction at the terminal alkyne in 85% yield (Table 1, entry 2). 6-Methoxy 2-naphthylacetylene reacted smoothly with **B** with an isolated yield of 86% (Table 1, entry 3). An *ortho* substitution of the methoxy group did not seem to alter the reactivity as 2-methoxy phenylacetylene furnished the coupling product in 78% yield (Table 1, entry 4). Analogously, 3,4,6-Trimethyl phenylacetylene afforded the aryl-alkyne product in 72% (Table 1, entry 5). Pleasingly, the electron-deficient substrate 4-cyano phenylacetylene also reacted efficiently in 85% yield (Table 1, entry 6). The presence of an electron-withdrawing *ortho*-formyl group did not

hamper the reaction and the corresponding aryl-alkyne was obtained in 67% yield (Table 1, entry 7). It is noteworthy that aliphatic alkynes were also potential coupling candidates as both *n*-hexyne and 1-phenyl prop-2-yne delivered the coupling products in 69% and 98% yields, respectively (Table 1, entries 8 and 9). A conjugated enyne such as ethynylcyclohexene also was tolerated and afforded the coupling product in a moderate 53% yield (Table 1, entry 10). It is remarkable that the (2-ethynylphenyl)methanol substrate having a potentially coordinating free hydroxy group selectively coupled with a reasonably good yield of 61% (Table 1, entry 11). It is to be noted that no self-coupling of aryl moieties from the gold complexes were observed in these reactions; this is attributed to the redox stability, which is typical for gold. A negligible amount of the alkyne homo-coupling product was observed in most of the cases. No coupling was observed when the reaction was run in the absence of the palladium catalyst.

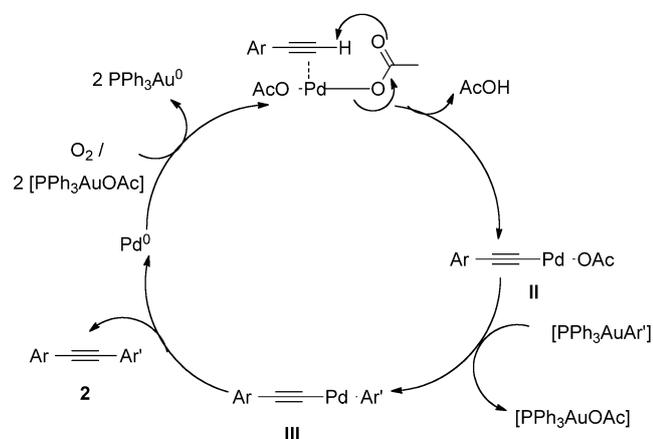
A handful of other gold complexes were also tested for their efficiency to undergo Sonogashira coupling with *para*-methoxy phenylacetylene as the standard coupling partner (Table 2, entries 1–9). The complexes (*para*-tolyl)(triphenylphosphanyl)gold^[11] (**C**) and (3,5-dimethyl)(phenyl-triphenylphosphanyl)gold^[12] (**D**) furnished the coupling product in excellent yields of 92% and 90%, respectively (Table 2, entries 1 and 2). The (1-naphthyl)(triphenylphosphanyl)gold^[13] compound (**E**) underwent the coupling reaction in a moderate 60% yield while the isomeric (2-naphthyl)(triphenylphosphanyl)gold^[13] complex (**F**) afforded the product in a good yield of 83% (Table 2, entries 3 and 4, respectively). The complex (anthracenyl)-(triphenylphosphanyl)gold (**G**) delivered the coupling product in 64% yield (Table 2, entry 5) and traces of liberated anthracene were found in the reaction mixture. A similar complex (1-pyrenyl)-(triphenylphosphanyl)gold^[14] (**H**) reacted with a moderate yield of 42% (Table 2, entry 6). The electron-rich complex (*ortho*-anisyl)(triphenylphosphanyl)gold (**I**) delivered the coupling product in 74% yield (Table 2, entry 7). The sterically demanding (2,4,6-trimethylphenyl)(triphenylphosphanyl)gold^[15] (**J**) also reacted well with an appreciable yield of 64% (Table 2, entry 8). The heterocyclic complex (2-furyl)(triphenylphosphanyl)gold^[16] (**K**) responded inefficiently to the coupling and the product was isolated in a mediocre 34% yield (Table 2, entry 9).

The mechanistic profile for this coupling could be rationalized in correlation with Hashmi's proposal for the palladium-catalyzed biaryl synthesis using organogold complexes.^[6a] The reaction is initiated by the coordination of the palladium catalyst to the alkyne to form the palladium(II)-acetylide intermediate **II** (Scheme 2).

Table 2. Exploration of different organogold complexes for the Sonogashira coupling.

Entry	Gold complex	T [h]	Product (2)	Yield [%]
1		C 1.5		92
2		D 2		90
3		E 2		60
4		F 1.5		83
5 ^[a]		G 1.5		64
6		H 2		42
7 ^[a]		I 2		74
8		J 2		64
9		K 2.5		34

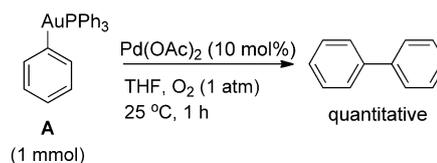
[a] The yield calculated from ¹H NMR spectra. The gold seemed to agglomerate to zero-valent clusters eventually, which explained the wine-red^[21] coating on the inner surface of the reaction flask after the reaction. Attempts to recover the gold by the addition of halogen donors such as LiCl, MgBr₂, or *N*-bromosuccinimide (NBS) proved futile.

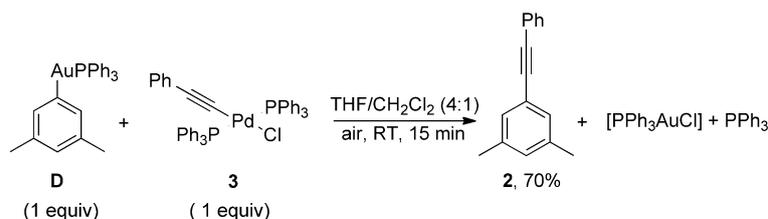


Scheme 2. Plausible mechanism for the reaction.

The mechanistic rationale for the formation of the palladium(II)-acetylide species is somewhat intriguing. Normally the formation of such a species is assisted by an external base, which is absent here (interestingly stoichiometric triethylamine did not have any significant influence on the reaction profile when added to the model reaction). We presume that the acetate ligand of the palladium catalyst would be acting as a base,^[4b,17,18] thus leading to the formation of the alkynyl-palladium species **II** (following an equimolar mixture of Pd(OAc)₂ and phenylacetylene in deuterated tetrahydrofuran by ¹H NMR spectroscopy showed that the acetylinic proton diminishes in intensity, while new signals typical for acetic acid increased in intensity, see the Supporting Information for details). The subsequent transmetalation from the gold complex furnishes the aryl-alkynyl palladium intermediate **III**.^[19] Subsequent reductive elimination and aerobic oxidation of the resulting palladium(0) species regenerates the catalyst. In line with a recent report from Gagné and Weber,^[20] we assume that the [PPh₃AuOAc] generated after transmetalation also acts as a co-oxidant for palladium. The possibility of a [Pd(OAc)Ar'] species formed by the previous transmetalation of Pd(OAc)₂ and the gold complex reacting with the alkyne to form the intermediate **III** was ruled out by a control experiment (Scheme 3), in which the gold complex **A** reacted with catalytic amounts of Pd(OAc)₂, thus furnishing the self-coupled biaryl in quantitative yields. The absence of such biaryl products in the Sonogashira reactions points to the assumption that the catalyst reacts preferentially with the alkyne to form the palladium(II)-acetylide species **II**.

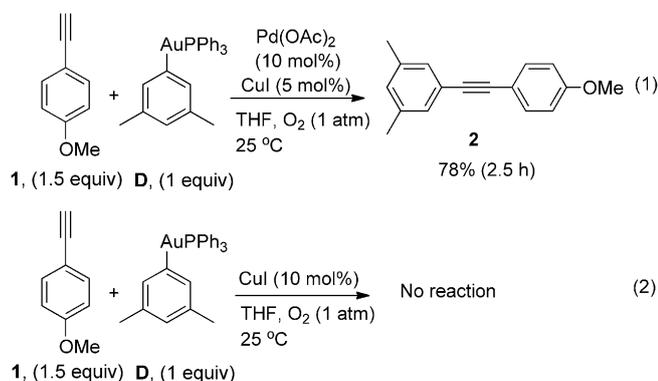
To support the intermediacy of the alkynyl-palladium(II) species **II**, we synthesized a model alkynyl-palladium(II) complex^[22] **3** and exposed it to the organogold complex **D** under identical conditions to the coupling reactions (Scheme 4). Pleasingly, the reaction was completed in 15 minutes, and the Sonogashira product **2** was isolated in 70% yield. The formation of (triphenylphosphine)gold(I) chloride was also observed in the ³¹P NMR spectrum, which further supported the transmetalation. The possibility of any copper impurities in the commercially available Pd(OAc)₂ that could catalyze/co-catalyze the reaction

Scheme 3. Self-coupling of organogold complex **A** with palladium catalyst.



Scheme 4. Coupling with palladium-alkynyl complex and organogold complex.^[a,b] [a] A small amount CH_2Cl_2 was used as a co-solvent to dissolve the palladium complex. [b] Yield calculated from ^1H NMR spectroscopy.

was ruled out by carrying out the model reaction in the presence of 5 mol% copper(I) iodide (Scheme 4, [Eq. (1)]). The reaction did not show any rate enhancement compared to the standard reaction (Table 2, entry 2). Expectedly, copper(I) iodide alone was not able to catalyze the reaction (Scheme 4, [Eq. (2)] and Scheme 5).



Scheme 5. Model reactions to rule out a copper-catalyzed pathway.

In conclusion, an effective procedure for an aerobic aryl-alkyne coupling under very mild conditions has been developed. The methodology explored the utility of organogold complexes as pseudo-aryl halides in the Sonogashira coupling and does not require any base, ligand, or inert conditions. Experimental support for the proposed mechanism was also gained. Current efforts are directed towards improving the system for the catalytic use of gold.

Experimental Section

The alkyne (1.5 mmol, 1.5 equiv) was added to dry THF (2 mL) in a flame dried round bottom flask. The gold complex (1 mmol, 1 equiv) was added and oxygen was bubbled through the solution for 2 min. Palladium acetate (10 mol%) was added and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by ^{31}P NMR spectroscopy until the gold complex was completely consumed (1.5–2.5 h). The solvent was removed under reduced pressure and the residue was purified over silica gel (hexane/ethyl acetate 100:1) to furnish the pure cross-coupled product.

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Keywords: alkynes • catalysis • cross-coupling • gold • palladium

- [1] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
- [2] a) *Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds* (Eds.: J. Lam, H. Bretler, T. Arnason, L. Hansen), Elsevier, Amsterdam, **1988**; b) Z. Novák, A. Kotschy, *Org. Lett.* **2003**, *5*, 3495.
- [3] a) J.-H. Li, Q.-M. Zhu, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393; b) J.-H. Li, D.-P. Wang, Y.-X. Xie, *Eur. J. Org. Chem.* **2005**, 4256; c) T. Fukuyama, M. Shinmen, S. Nishitani, *Org. Lett.* **2002**, *4*, 1691; d) Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 379; e) L. Anastasia, E. Negishi, *Org. Lett.* **2001**, *3*, 3111; f) S. Cacchi, G. Fabrizi, L. M. Parisi, *Org. Lett.* **2003**, *5*, 3843; g) S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752; h) M. B. Thathagar, J. Beckers, G. Rothenberg, *Green Chem.* **2004**, *6*, 215; i) K. Okuro, M. Furuune, M. Enna, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 4716; j) B.-X. Tang, F. Wang, J.-H. Li, Y.-X. Xie, M.-B. Zhang, *J. Org. Chem.* **2007**, *72*, 6294; k) C. G. Bates, P. Saejueng, J. M. Murphy, D. Venkataraman, *Org. Lett.* **2002**, *4*, 4727; l) Y. F. Wang, W. Deng, L. Liu, Q. X. Guo, Chin, *Chem. Lett.* **2005**, *16*, 1197; m) J.-H. Li, J.-L. Li, D.-P. Wang, S.-F. Pi, Y.-X. Xie, M.-B. Zhang, X.-C. Hu, *J. Org. Chem.* **2007**, *72*, 2053; n) D. Ma, F. Liu, *Chem. Commun.* **2004**, 1934; o) J. Mao, J. Guo, S.-J. Ji, *J. Mol. Catal. A* **2008**, *284*, 85; p) M. Wu, J. Mao, J. Guo, S. Ji, *Eur. J. Org. Chem.* **2008**, 4050; q) F. Monnier, F. Turtaut, L. Duroire, M. Taillefer, *Org. Lett.* **2008**, *10*, 3203; r) M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940; *Angew. Chem. Int. Ed.* **2008**, *47*, 4862; s) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *38*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954;
- [4] a) L. K. Hwang, Y. Na, J. Lee, Y. Do, S. Chang, *Angew. Chem.* **2005**, *117*, 6322; *Angew. Chem. Int. Ed.* **2005**, *44*, 6166; b) X. Wang, W. Qin, N. Kakusawa, N. Yasuike, J. Kurita, *Tetrahedron Lett.* **2009**, *50*, 6293; c) B. Panda, T. K. Sarkar, *Chem. Commun.* **2010**, *46*, 3131.
- [5] Fuchitha et. al, observed for the first time that the arylgold complexes couple with phenylacetylene to form aryl-alkynes. Only two examples were given. See; a) Y. Fuchita, Y. Utsunomiya, M. Yasutake, *J. Chem. Soc. Dalton Trans.* **2001**, 2330.
- [6] For reports on organogold complexes employed in coupling reactions, see; a) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi, F. Rominger, *Angew. Chem.* **2009**, *121*, 8392; *Angew. Chem. Int. Ed.* **2009**, *48*, 8243; b) Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc.* **2009**, *131*, 18022; c) Y. Shi, S. D. Ramgren, S. A. Blum, *Organometallics* **2009**, *28*, 1275; d) A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 1307; e) M. Peña-Lopez, M. Ayán-Varela, L. A. Sarandeses, J. Perez Sestelo, *Chem. Eur. J.* **2010**, *16*, 9905; f) J. J. Hirner, S. A. Blum, *Organometallics* **2011**, *30*, 1299.
- [7] For relevant reports on gold mediated/co-catalyzed Sonogashira couplings, see; a) L. A. Jones, S. Sanz, M. Laguna, *Catal. Today* **2007**, *122*, 403; b) A. Corma, C. González-Arellano, M. Iglesias, S. Pérez-Ferreras, F. Sánchez, *Synlett* **2007**, 1771; c) C. González-Arellano, A. Abad, A. Corma, H. García, M. Iglesias, F. Sánchez,

- Angew. Chem.* **2007**, *119*, 1558; *Angew. Chem. Int. Ed.* **2007**, *46*, 1536; d) C. González-Arellano, A. Corma, M. Iglesias, F. Sánchez, *Eur. J. Inorg. Chem.* **2008**, 1107; e) H. Plenio, *Angew. Chem.* **2009**, *121*, 3158; *Angew. Chem. Int. Ed.* **2009**, *48*, 3112; f) B. Panda, T. K. Sarkar, *Tetrahedron Lett.* **2010**, *51*, 301.
- [8] Echavarren has recently proved the unlikeliness of a palladium-free Sonogashira coupling reaction, see; T. Lauterbach, M. Livendahl, A. Rosellon, P. Espinet, A. M. Echavarren, *Org. Lett.* **2010**, *12*, 3006.
- [9] For relevant reports on gold-catalyzed Sonogashira products, see; a) T. de Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513; b) M. N. Hopkinson, J. E. Ross, G. T. Giuffredi, A. D. Gee, V. Gouverneur, *Org. Lett.* **2010**, *12*, 4904.
- [10] G. Calvin, G. E. Coates, P. S. Dixon, *Chem. Ind.* **1959**, 1628.
- [11] K. E. Roth, S. A. Blum, *Organometallics* **2010**, *29*, 1712.
- [12] A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592.
- [13] M. Osawa, M. Hoshino, D. Hashisume, *Dalton Trans.* **2008**, 2242.
- [14] CCDC 800283 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [15] C. Croix, A. Balland-Longeau, A. Allouchi, M. Giorgi, A. Duchene, J. Thibonnet, *J. Organomet. Chem.* **2005**, *690*, 4835.
- [16] K. A. Porter, A. Shier, H. Schmidbaur, *Organometallics* **2003**, *22*, 4922.
- [17] Trost has reported the formation of alkynylpalladiums in the absence of an external base. See; a) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms, G. Rühler, *J. Am. Chem. Soc.* **1997**, *119*, 698; b) B. M. Trost, J.-P. Lumb, J. M. Azzarelli, *J. Am. Chem. Soc.* **2011**, *133*, 740.
- [18] For a review on carboxylate assisted C–H activation of arenes, see: L. Ackerman, *Chem. Rev.* **2001**, *101*, 1315.
- [19] The organogold complexes are known to undergo protodeauration in the presence of Brønsted acids. We have tested the stability of model complex **B** in the presence of stoichiometric acetic acid and found that it is considerably stable (decomposed in 3 h at room temperature) over the reaction time for the coupling (1.5 h). For a detailed study of relative basicities of organogold complexes, see: Ref. [11].
- [20] D. Weber, M. Gagné, *Chem. Commun.* **2011**, *47*, 5172.
- [21] H. Miyamura, R. Matsubara, Y. Miyazaki, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 4229–4232; *Angew. Chem. Int. Ed.* **2007**, *46*, 4151–4154.
- [22] Y. Izawa, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2033.

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