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Unlikeliness of Pd-Free Gold(I)-Catalyzed Sonogashira Coupling Reactions

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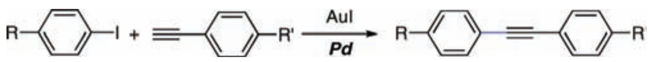
ABSTRACT



The Sonogashira coupling reaction is not catalyzed by AuI/dppe in the absence of Pd complexes. However, addition of 0.1 mol % of Pd(0) led to efficient cross-coupling reactions. The most plausible catalytic cycles for the Au-catalyzed cross-coupling reactions have been examined and are unlikely in the absence of Pd contamination.

In the past decade gold has been shown to promote a bewildering variety of metal-catalyzed processes to the point that it would seem that other transition metals are being forced to retreat.[1] Most Au(I)-catalyzed reactions of alkynes and allenes do not involve any change in oxidation state of the gold center, which acts essentially as a tunable acidic center throughout the reaction.[2]

There are other processes where gold is reported to do the job usually carried out with palladium, producing C−C cross-coupling.[3] This is, for instance, the case of gold-catalyzed Sonogashira[4−7] and Suzuki[4,8,9] reactions. For the standard reaction of phenylacetylene and iodobenzene, with PhI, Au(III) led only to homocoupling of the acetylene in low yield,[4,10] whereas [AuCl(PPh_3)] (20 mol %) gave the coupling product (tolane) in 54% conversion (xylene, 130 °C, 24 h).[4]

It has been argued that “Au(I) with the same d^{10} configuration as Pd(0) can catalyze reactions typically catalyzed by palladium”,[4,9] but this statement is too simple. For instance, Pt(0) does not catalyze many reactions typically catalyzed by Pd(0),[11] showing that isoelectronic metal centers do not necessarily behave similarly.

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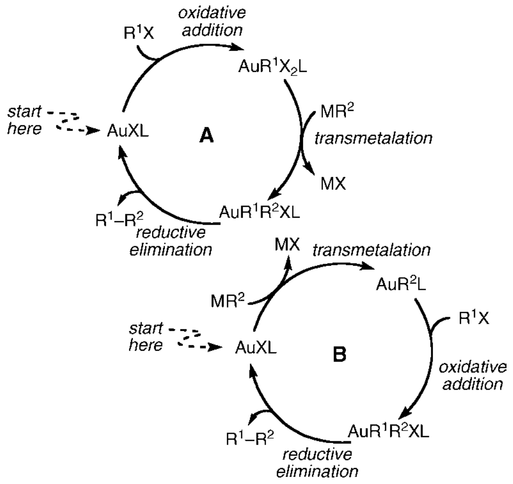
Experimental reports claim that Au(I) is selective and very active, for instance, toward cross coupling of aryl halides with acetylenes ("Pd-free Sonogashira" for example), in the presence of mild bases. Surprisingly, this intriguing process has not been investigated mechanistically. We decided to set out experiments that would explain mechanistically the Pd-free cross-coupling catalysis with gold, but in fact what we are reporting is our failure to find a plausible mechanism. Furthermore, our experiments suggest that the presence of adventitious Pd might explain the positive "Pd-free Sonogashira" catalysis reported. This is in line with recent findings in Suzuki coupling reactions, which proceed under very low Pd loadings.[12,13]

At first sight it looks reasonable to consider that a similar d^{10}/d^8 interplay might be operative for the two isoelectronic couples Pd(0)/Pd(II) and Au(I)/Au(III). Both d^8 metal centers not only are isoelectronic, they also form square-planar complexes. For the d^8 metal centers, Au(I) is usually linear coordinated. Although Pd(0) with common ligands (PPh_3) is tetrahedral, it is known to dissociate in solution and it is believed that the reactive species are dicoordinated PdL_2.[14] Thus, the typical oxidative addition/transmetalation/reductive elimination cycle of Pd, which applies (in a general sense) to any Pd-catalyzed cross-coupling process, could in principle be taken as the model for gold cross-coupling catalysis. However, there is an important difference in the lower oxidation state of the two systems: whereas for PdL_2 only the oxidative addition reaction is expected, for AuXL both oxidative addition and transmetalation reactions are plausible.[15,16] Therefore, two cycles should be considered where these two steps are transposed (Scheme 1, cycles A and B).[17,18] The feasibility of the two cycles and their steps as isolated processes was experimentally investigated, starting with [AuI(PPh_3)].

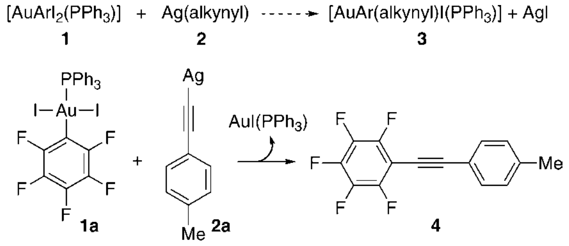
Scheme 1. Plausible Cycles for Au-Catalyzed Cross-Coupling Reactions[a]



[a] Here R^1 = aryl and R^2 = alkynyl.

Both cycles A and B have in common the third step, the reductive elimination from the Au(III) intermediate [AuAr(alkynyl)XL]. No complex of this kind has been reported, so we decided to check the transmetalation reaction between an aryl−Au(III) complex **1** and a silver alkynyl derivative **2** for the in situ formation of a complex **3** of this type (Scheme 2). Thus, the stable complex *trans*-[Au(C_6F_5)I_2(PPh_3)] (**1a**)[19] was treated with Ag($C_2C_6H_4Me$) (**2a**) (1:1) in order to exchange one iodide by one alkynyl, but the corresponding complex could not be obtained. Instead, the cross-coupling product **4** was obtained showing that the coupling step on Au(III), common to both cycles, not only is feasible but is also a very fast process.[20] In other words, if the two previous steps in the cycle take place, the cross-coupling product should be formed immediately.

Scheme 2



Cycle A: The first step in this cycle is the oxidative addition of ArX to [AuX(PPh_3)] to give Au(III) complexes

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(11) See, for example: (a) Mateo, C.; Fernández-Rivas, C.; Cárdenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *17*, 3661–3669. (b) Nilsson, P.; Puxty, G.; Wendt, O. F. *Organometallics* **2006**, *25*, 1285–1292.

(12) (a) Up to the level of 50 ppb Pd found in commercially available Na_2CO_3 catalyzed the Suzuki coupling reaction of phenylboronic acid with 4-bromoacetophenone: Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161–168.

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(17) X^- stands for an inorganic anionic ligand, often a halide. Note that (i) the X group coming with the electrophile R^1X can be different from the X ligand coming with the gold complex and (ii) anionic ligands undergo fast exchange in solution so that, when two or more were present on the metal, we should represent the different combinations in, for instance, AuX_3. However, these possible changes are not decisive for the discussion.

(18) Aryl−Au(I) complexes catalyze the isomerization of *trans*-[PdR$_2$L$_2$] to *cis*-[PdR$_2$L$_2$] complexes by Au(I)/Pd(II) transmetalation: Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 3677–3683.

(19) Usón, R.; Laguna, A.; Pardo, J. *Syn. React. Inorg. Met.-Org. Chem.* **1974**, *4*, 499–513.

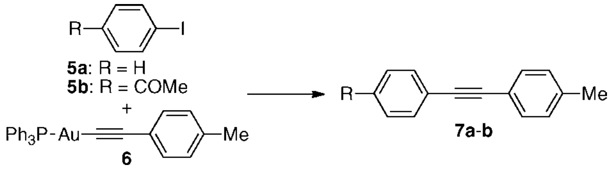
(20) This result is in keeping with that observed in the reaction between [AuPhCl$_2$(lut)] or [Au(2,5-Me$_2$C$_6$H$_3$)Cl$_2$(lut)] (lut = 2,6-dimethylpyridine) and phenylacetylene: Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330–2334.

[$AuArX_2(PPh_3)$]. Complexes of this kind are stable with perhalogenated aryls such as C_6F_5, but not for conventional aryl groups.[21,22] They are obtained by oxidative addition of Au(I) complexes with X_2 (X = Cl, Br, I). To the best of our knowledge, there is no report for a successful oxidative addition of ArX to [AuXL], which is the requirement of the first step of cycle A. In fact all attempts to carry out the oxidative addition of PhI, *p*-$MeOC_6H_4I$, *p*-$MeOCC_6H_4I$, or *p*-$O_2NC_6H_4I$ to [$AuCl(PPh_3)$] in a variety of solvents at 40−80 °C led to complete recovery of the starting materials. Indeed, only methyl gold(I) complexes [$AuMePR_3$] (PR_3 = PMe_3, PMe_2Ph, $PMePh_2$, PPh_3) are known to undergo slow oxidative addition reaction with alkyl iodides, following the expected pattern for S_N2 reactions: $CH_3I > EtI >$ *i*-PrI.[23]

This behavior clearly differs from that of [$Pd(PPh_3)_4$] or [$Pd_2(dba)_3$] + PPh_3 systems, which are easily oxidized by aryl halides to give complexes [$PdRX(PPh_3)_2$].[24] It seems that the oxidation potentials of the isoelectronic d^{10} complexes of Au(I) and Pd(0) differ significantly, enough as to prevent the oxidation to Au(III) by ArX. Therefore, the viability of cycle A is discarded because the initial step (oxidative addition to [$AuI(PPh_3)$]) does not seem feasible.

Cycle B: The formation of [Au(alkynyl)(PPh_3)] in the catalytic cycle would require the alkynylation of [$AuI(PPh_3)$] with acetylenes in the presence of base. This reaction is well-known to occur easily and to be fast and complete.[25] It has been used, for instance, to prepare gold liquid crystals,[26] and takes place also with the starting complexes implicated in the catalysis under examination. A mild base (e.g., NaOAc) is enough to promote the reaction, which even proceeds in the absence of base.[26] Indeed complex [$Au(C_2C_6H_4Me)(PPh_3)$] (**6**) was easily prepared and the oxidative addition reactions with RC_6H_4I (R = Ph (**5a**), COMe (**5b**)) under different conditions were studied. As discussed above, if an oxidative addition [$AuR(C_2C_6H_4Me)I(PPh_3)$] product was formed it should give rise immediately to the heterocoupling product. As shown in Table 1 (entries 1−5), in no case was coupling product observed regardless of the R group and the reaction conditions. This is a strong indication that, similarly to [$AuI(PPh_3)$], also [$Au(C_2C_6H_4Me)(PPh_3)$] is resistant to oxidative addition by ArI and frustrates the coupling cycle.

Table 1. Oxidative Addition Reactions of **5a**,**b** under Different Conditions



entry	5	conditions	additive	yield (%)
1	**5a**	toluene, 130 °C, 24 h		<1%
2	**5a**	toluene, 300 °C,[a] 24 h		<1%
3	**5a**	PhI solvent, 30 °C, 24 h		<1%
4	**5a**	toluene, 130 °C, 24 h	K_2CO_3	<1%
5	**5b**	toluene, 130 °C, 24 h		<1%
6	**5b**	toluene, 130 °C, 16 h	[Pd][b]	**7b** 100%

[a] Microwave heating. [b] [Pd] = [$PdCl_2(PPh_3)_2$] (1.4 mol %), *i*-Pr_2NH.

Interestingly, the addition of a catalytic amount of Pd complex (entry 6) suffices to produce complete conversion, suggesting again that Pd performs easily the oxidative addition that Au does not. In these conditions the gold alkynyl would simply be an intermediate agent transmetalating the nucleophile (alkynyl in this case) to Pd. In other words, the reaction would be a common Sonogashira reaction catalyzed by Pd, with Au(I) playing the role classically played by Cu(I). In coincidence with this interpretation, the gold(I) complex [AuCl(tht)] (tht = tetrahydrothiophene) has been shown to replace Cu(I) as cocatalyst in Sonogashira reactions catalyzed by [$PdCl_2(PPh_3)_2$].[27] It is important to note that [AuCl(tht)] was inactive in the absence of a Pd complex.[27a]

According to our results, gold should not be able to catalyze the so-called Pd-free Sonogashira coupling, since Au(I) is unable to activate the electrophile ArI by undergoing oxidative addition. This conclusion is in contrast with recent reports of reactions that give excellent yields.[5,6] Consequently we decided to check their reproducibility in the reaction between aryl iodide **5b** and tolylacetylene (**8**).[28] In our hands, only traces of the coupling product **7b** were produced using AuI (Table 2).

The material reported to be catalytically active in the Sonogashira and Suzuki coupling reactions[5] was mistakenly assigned as complex **9**, formed from monoimine **10** (Figure 1).[29] In our hands, treatment of [$AuCl(PPh_3)$] with the potassium salts of any of the ligands probably present in

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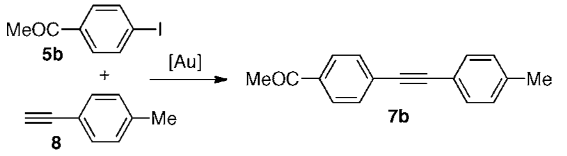
(28) As a control, this Sonogashira reaction proceeds with $PdCl_2(PPh_3)_2$ (1 mol %) and [$AuCl(PPh_3)$] (1 mol %) or $AuCl_3$ (1 mol %) to give **7b** in 72% and 63% yield (determined by GC-MS), respectively.

Table 2. Effect of Palladium on the Sonogashira Coupling with AuI/dppe[a]



entry	$[Pd]^b$ (mol %)	conversion (%)	yield (%)
1		<2%	<2%
2	1.2×10^{-4}	6	6
3	1.2×10^{-3}	16	16
4	1.2×10^{-2}	24	24
5	0.12	100	82
6	1.2	100	78
7[c]	1.2	<2%	<2%

[a] AuI (2 mol %), dppe (2 mol %), K_2CO_3, toluene, 130 °C, 16 h. [b] [Pd] = $[Pd_2(dba)_3 \cdot CHCl_3]$. [c] Room temperature.

those studies (monoimine **10** and bisimine **11**) resulted only in mixtures of Au(I) complexes that did not catalyze the Sonogashira coupling of iodobenzene with phenylacetylene.

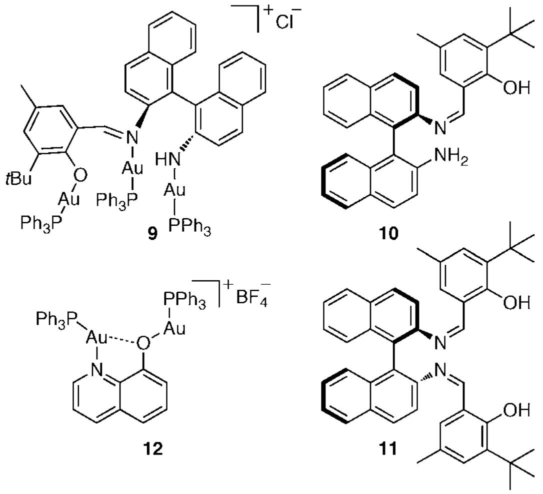


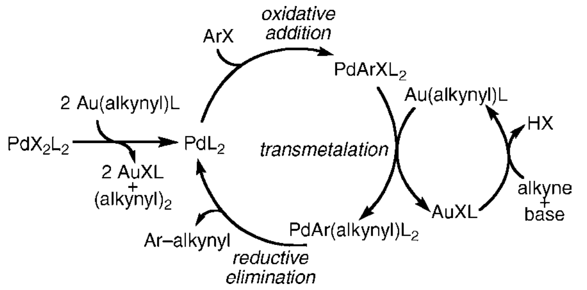
Figure 1. Compounds **9**−**12**.

Since Au(I) complexes with Au−O bonds are a rarity, we also examined the activity of the well-characterized complex **12**,[30] containing N−Au and O−Au bonds as had been proposed for **9**. No coupling between **8** or *p*-acetylphenylacetylene with 1-iodo-4-methylbenzene was observed with **12** (10 mol %) (K_2CO_3, toluene, 130 °C, 16 h) in the presence or absence of $[Pd_2(dba)_3 \cdot CHCl_3]$.

Even high-purity gold often contains traces of palladium,[31] which leads us to suspect that the presence of traces of palladium is responsible for the success of the Au(I)-catalyzed "Pd-free Sonogashira reaction". The gold iodide used in this work contained 3.1 μg/g Pd in AuI and was practically inactive in the Sonogashira reaction, but adding small amounts of Pd(0) increased progressively the yield of the Sonogashira product (Table 2).

Since a metal catalyst M for cross-coupling processes is required to activate the electrophile RX by undergoing oxidative addition to form RMX, it is unlikely that these processes can be catalyzed by metal centers that cannot undergo such oxidation, as seems to be the case for Au(I) with aryl halides. The Au-catalyzed Sonogashira reactions reported might well proceed thanks to Pd contamination of any of the compounds involved in the reaction, which would provide the Pd catalyst necessary to carry out the reaction according to Scheme 3. The catalysis would fail or succeed in different hands depending on the amount of Pd contamination in the reagents used. Pd contamination should be tested before a Pd-free catalysis is claimed.

Scheme 3



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Supporting Information Available: Experimental details, characterization data, and additional results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Complex **9** was depicted in refs 5a and 5c with different formulas ($[(C_{32}H_{28}N_2)O\{Au(PPh_3)_3\}]Cl$ or $[(C_{32}H_{30}N_2)O\{Au(PPh_3)_3\}]$, respectively). Examination of the ^1H NMR spectrum of the starting ligand used for the preparation of **9** in those references, kindly provided by the authors, revealed that it was in fact the bisimine **11**.

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