Gold and Palladium Combined for the Sonogashira Coupling of Aryl and Heteroaryl Halides

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Abstract: A highly efficient gold and palladium combined methodology for the Sonogashira coupling of a wide array of electronically and structurally diverse aryl and heteroaryl halides is described. The orthogonal reactivity of the two metals shows high selectivity and extreme functional group tolerance in Sonogashira coupling. A brief mechanistic study reveals that the gold acetylide intermediate enters into the palladium catalytic cycle at the transmetalation step.

Key words: gold catalysis, cross-coupling, Sonogashira coupling, gold–palladium combined

Among all C–C bond-forming reactions now in use, the Sonogashira reaction[1] undeniably occupies the number one position in terms of its efficiency for accessing arylalkynes and conjugated enynes, which are prevalent intermediates for the synthesis of a diverse array of natural products, pharmaceuticals, and molecular organic materials.[2] The traditional experimental procedure involves $PdCl_2(PPh_3)_2$ as a palladium(0) precursor and copper(I) iodide as a co-catalyst in a solution containing an amine base;[3,4] copper(I) iodide is required to activate the alkynes as a π-acid. The addition of copper salts as co-catalysts in the typical Sonogashira cross-coupling is not without drawbacks. In particular, the in situ generation of copper acetylides under the reaction conditions often gives rise to homocoupling products of the terminal alkyne (the so-called Glaser coupling),[5] along with the main reaction product, upon exposure to oxidative agents or air. This side reaction is especially undesirable when the terminal acetylene is difficult to obtain or expensive. Thus, over the years various alternatives to the copper(I) 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 salts[6] as activators or the use of palladium-only procedures.[7] Clearly, the development of a new co-catalyst other than copper salts, e.g. copper(I) iodide, that will not allow homocoupling as a side reaction is desirable.

During the last decade, cationic phosphine–gold(I) complexes have found extensive use as versatile and selective catalysts for a growing number of synthetic transformations.[8,9] The alkynophilicity of cationic gold(I) species is superior to that of other coinage metals, for example, copper and silver. Thus it is conceivable that replacement of the copper(I) co-catalyst by cationic gold(I) would not only promote the Sonogashira-type cross-coupling reaction of aryl halides with alkynes, but also the extreme resistance of gold compounds to oxidation would mean that these reactions are unlikely to be accompanied by the usual Glaser-type products that are frequently observed in copper co-catalytic processes. As there is an ongoing interest in methods for C–C bond formation taking advantage of the synergy between gold and palladium catalysts, it occurred to us that the orthogonal reactivity of the two metals may show high selectivities in Sonogashira coupling. Indeed, the first gold–palladium dual catalytic Sonogashira coupling of aryl halides was reported by Laguna and co-workers[10] The gold compounds AuCl(tht), $AuCl(PPh_3)$, and $Na[AuCl_4]$ were used as co-catalysts in Sonogashira-type cross-coupling reactions (tht = tetrahydrothiophene). In these reactions, phenylacetylene was used as the alkyne source, tetrahydrofuran as the solvent, and diisopropylamine as the base. It was found that $Na[AuCl_4]$ and AuCl(tht) are efficient co-catalysts in palladium-catalyzed alkynylation reaction. Laguna et al. observed full conversion for aryl iodides at room temperature and for activated aryl bromides under reflux conditions. On the other hand, reactions with non-activated aryl bromides proceed in poor yields. They also reported that identical experiments with hexyne in place of phenylacetylene also gave poor yields (<10%), showing that the gold co-catalysts used are much more efficient in activating arylalkynes than alkylalkynes. Furthermore, use of a different gold co-catalyst, $AuCl(PPh_3)$, was shown to be practically ineffective (<1% conversion) even in the case of an electron-poor aryl iodide, 4-iodoacetophenone (**1a**) (Scheme 1).

As part of a broader program on the unique reactivity of Pd–Au dual catalytic systems,[11] we have had cause to reinvestigate[12] the Sonogashira-type cross-coupling of 4-iodoacetophenone (**1a**) with phenylacetylene using a combination of $PdCl_2(PPh_3)_2$ and $AuCl(PPh_3)$ strictly under the conditions of Laguna and co-workers. The result was dramatic (Scheme 1): the product alkyne **2a** was obtained in excellent yield (92%) (96% conversion)! 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.

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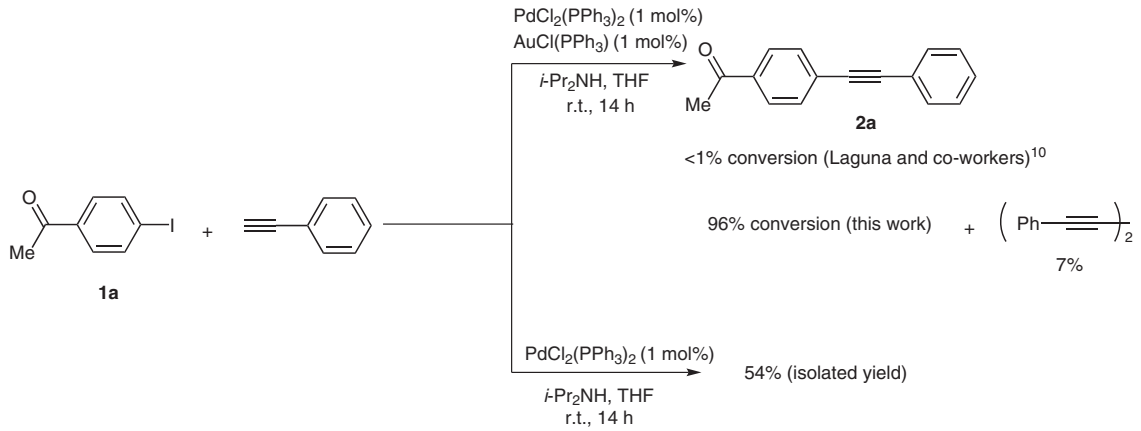
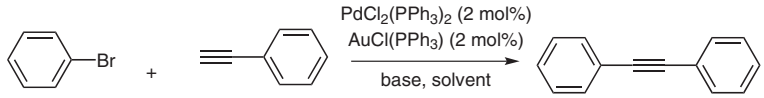


Scheme 1 Reinvestigation of the work of Laguna et al.

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 (**1b**) with phenylacetylene as a model reaction and the results are presented in Table 1. Clearly, the catalytic system is not sufficiently powerful to allow reaction in tetrahydrofuran at ambient temperature; heating to reflux was required in this case, although prolonging heating (>4 h) did not increase the yield of the reaction further (entries 1 and 2). The reaction also takes place in water or triethylamine, but the yields are unsatisfactory (entries 3 and 4). Finally, going from tetrahydrofuran through acetonitrile, dimethyl sulfoxide, and *N*,*N*-dimethylformamide, and changing the base from triethylamine to potassium carbonate allowed identification of the efficient catalytic system for the Sonogashira-type coupling of bromobenzene (**1b**) as $PdCl_2(PPh_3)_2$/$AuCl(PPh_3)$ in *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide (DMA) in the presence of triethylamine (entries 8 and 10).

Under our optimized reaction conditions, we accomplished Sonogashira-type cross-coupling of a wide array of electronically and structurally diverse aryl and heteroaryl halides. With respect to the aryl bromides[13] and iodides,[14] both electron-neutral and electron-poor aryl halides **1a**–**c**,**f** react with alkynes to provide the corresponding products **2a**,**b**,**e**,**f** in excellent yields (Table 2,

Table 1 Effect of the Reaction Conditions on the Cross-Coupling of Bromobenzene with Phenylacetylene[a]



1b **2b**

Entry	Solvent	Base	Temp (°C)	Time (h)	Yield[b] (%)
1	THF	Et_3N	r.t.	8	–[c]
2	THF	Et_3N	reflux	4	81
3	H_2O	Et_3N	80	12	40
4	Et_3N	Et_3N	80	6	67
5	PhMe	Et_3N	80	6	33
6	MeCN	Et_3N	80	4	84
7	DMSO	Et_3N	80	3	89
8	DMF	Et_3N	80	3	96
9	DMF	K_2CO_3	80	3	79
10	DMA	Et_3N	80	3	96

[a] Reaction conditions: bromobenzene (**1b**, 1 mmol), phenylacetylene (1.1 mmol), base (3 mmol), solvent (3 mL).
[b] Isolated yield.
[c] No reaction.

entries 1, 2, and 5–7). Electron-rich aryl halides **1d**,**g** (entries 3, 8, and 9) are amenable to this protocol; however, more notable is that even highly electron-rich systems **1h**–**l** (entries 10–14) couple efficiently with alkynes. This method is also tolerant of *ortho*-substitution in aryl bromides **1m**–**o** (entries 15–18). Even the highly sterically hindered aryl halides **1e**,**p** (entries 4 and 19) couple with alkynes without difficulty.

Interestingly, several examples (Table 2, entries 3, 6, 9, 16, and 18) in which alkylalkynes are found to couple efficiently with aryl halides are also in conflict with the findings of Laguna and co-workers that the gold co-catalysts used in their work are much more efficient in activating arylalkynes than alkylalkynes.[10]

Notably, amino groups are tolerated under these conditions. 2-Bromoaniline (**1q**) and 2-bromo-4-methylaniline (**1r**) react with phenylacetylene to furnish the corresponding coupled products **2r** and **2s**, respectively, in good yields (Table 2, entries 20 and 21) uncontaminated by traces of cyclized products, e.g. indoles. It is well known that terminal alkynes bearing electron-withdrawing groups directly attached to the ethynyl carbon atom undergo side reactions such as Michael addition or self condensation under the classical Sonogashira reaction conditions. Thus, the Sonogashira coupling of aryl halides with highly electron-deficient terminal alkynes is a challenging case.[15] In order to address this problem, Taran et al. have developed a Pd–Ag protocol[16] for the cross-coupling of (trialkylsilyl)alkynes bearing an electron-withdrawing group, such as (trimethylsilyl)propiolate with aryl and heteroaryl iodides in the presence of a fluoride source. The disadvantages here are two-fold: high loading of the catalysts [Pd (10%), silver (20%)] and that the protocol needs preparation of (trialkylsilyl)propiolates from propiolates. As can be seen from Table 2, both bromobenzene (**1b**) and 4-bromotoluene (**1g**) couple nicely with methyl propiolate and furnish good yields of coupled products **2t**,**u** (entries 22 and 23). It may be noted that when propiolates are the alkyne partners, we used potassium or cesium carbonate as the base rather than triethylamine as the latter destroys the propiolic ester exothermally. Between potassium and cesium carbonate, the more basic cesium carbonate gives somewhat better results (70%) compared to potassium carbonate (60%) (entry 23). Note that no trace of the desired products is obtained from the cross-coupling of 4-bromo- or even 4-iodotoluene and methyl propiolate under classical Pd–Cu catalytic conditions. It is probable that the lower carbophilic Lewis acidity of copper(I) compared to gold(I) does not allow binding of the former with the electron-deficient alkyne, which is the necessary requisite for acetylide formation.

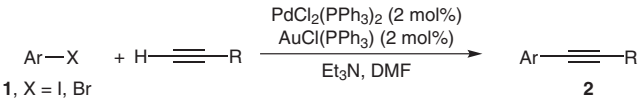
As can be seen from Table 2, entry 24, 2-bromophenol (**1s**) couples with phenylacetylene to afford the corresponding 2-alkynylphenol **2v**; no cyclized products, for example benzofuran, form under these conditions. Note that benzofuran is the sole product under the classical Pd–Cu-coupling conditions. An azide group is also nicely tolerated in our Pd–Au dual catalytic conditions. For example, 2-bromobenzyl azide (**1t**) couples with phenylacetylene to give the desired product **2w** in 92% yield unaccompanied by any undesired cyclized products (entry 25). A bromobenzene containing an imino group **1u** nicely couples with phenylacetylene thereby furnishing the desired 2-alkynylimine derivative **2x** uncontaminated with any trace of undesired isoquinoline derivatives (entry 26). It is well known that thiophenes are poor substrates in cross-coupling reactions. It is noteworthy that 2,3,4-tribromothiophene (**1v**) couples nicely under these conditions with excess phenylacetylene to yield the trialkynyl derivative **2y** (entry 27). Similarly, 1,3,5-tribromobenzene (**1w**) also couples satisfactorily with phenylacetylene to furnish the star-like trialkyne **2z** (entry 28) in excellent yield.

Our next goal was to probe the efficacy of our methodology for the alkynylation of unprotected 8-brominated adenosines and guanosines. It may be noted that Fairlamb et al. pioneered the alkynylation of unprotected 8-brominated adenosines and guanosines by a modified Sonogashira process.[17] As can be seen from Table 2 (entries 29 and 30), the Sonogashira coupling of 8-bromoadenosine (**1x**) and 8-bromoguanosine (**1y**) with phenylacetylene at 80 °C gives the desired 8-alkynylated products **2aa** and **2ab** in good yields. In terms of yields, our work is comparable to those of Fairlamb et al., but the advantages of our conditions are lower temperatures (120 °C vs. 90 °C) and reaction times (18 h vs. 5 h).

After successful Sonogashira coupling with aryl iodides as well as aryl bromides, our next task was to study the possibility of cross-coupling alkynes with aryl and heteroaryl chlorides. Thus, an electron-poor heteroaryl chloride, 2-chloro-4,6-dimethylpyridine-3-carbonitrile (**3a**), was found to react with phenylacetylene to furnish the coupled product **4a** in excellent yield (Table 3, entry 1). Also, 2-chloropyridine-3-carbaldehydes **3b** and **3c** (entries 2–5), reacted with various terminal alkynes to give the coupled products, formyl-substituted alkynes **4b**–**e** in good to excellent yields; note that these formyl-substituted alkynes were used for the synthesis of quinolines via gold-catalyzed benzannulation reactions.[18]

Aliphatic terminal acetylenes also couple with 2-chloro-4,6-dimethylpyridine-3-carbaldehyde (**3b**) without formation of any allenic product (Table 3, entry 5). Notably, the mildness of the reaction conditions can be gleaned from the fact that no further reaction (e.g., benzannulation[18,19]) occurred between the Sonogashira product, that is the formyl-substituted alkyne, and the excess alkyne present in the reaction mixture. Not only that, no trace of alkynylisochromene formed from the reaction of the Sonogashira product (formyl-substituted alkyne) with the terminal alkyne in the presence of a base. It may be noted that alkynylisochromenes are frequently formed in gold-catalyzed reactions of formyl-substituted alkynes with terminal alkynes in the presence of a catalytic amount of amine base.[20]

Table 2 Sonogashira Coupling of Aryl or Heteroaryl Iodides and Bromides with Terminal Alkynes[a]



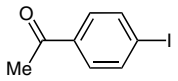
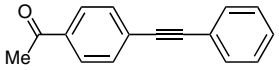
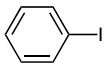
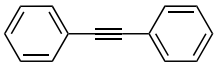
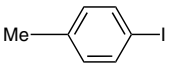
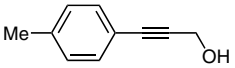
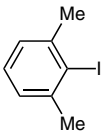
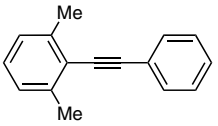
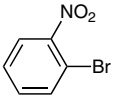
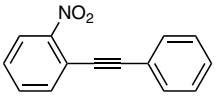
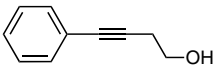
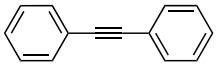
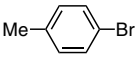
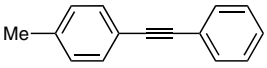
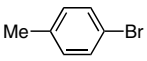
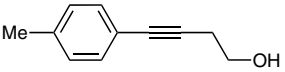
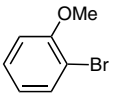
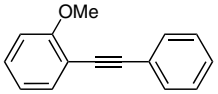
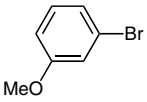
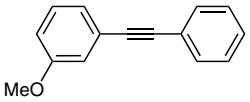
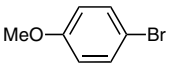
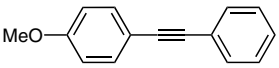
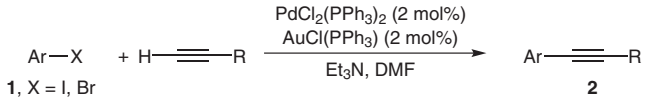
Entry	ArX	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	 **1a**	60	0.75	 **2a**	93
2	 **1c**	70	0.5	 **2b**	98
3	 **1d**	70	0.75	 **2c**	92
4	 **1e**	80	1	 **2d**	98
5	 **1f**	70	1	 **2e**	93
6	 **1b**	80	3	 **2f**	91[c]
7	 **1b**	80	3	 **2b**	96
8	 **1g**	80	3	 **2g**	94
9	 **1g**	80	3	 **2h**	91
10	 **1h**	80	7	 **2i**	91 (42)[d]
11	 **1i**	80	7	 **2j**	93
12	 **1j**	80	7	 **2k**	94

Table 2 Sonogashira Coupling of Aryl or Heteroaryl Iodides and Bromides with Terminal Alkynes[a] (continued)



1, X = I, Br **2**

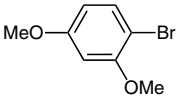
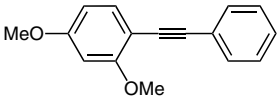
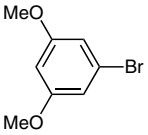
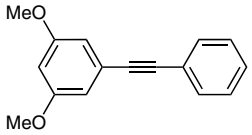
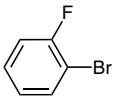
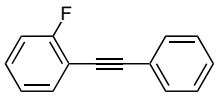
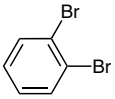
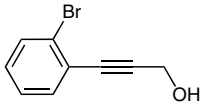
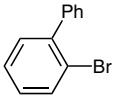
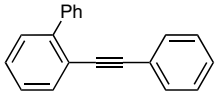
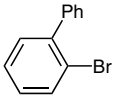
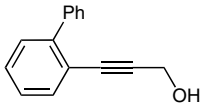
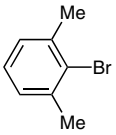
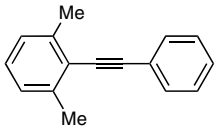
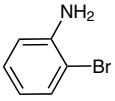
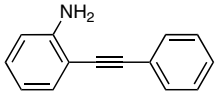
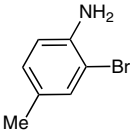
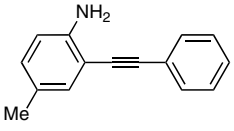
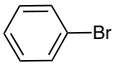
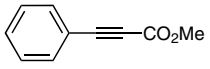
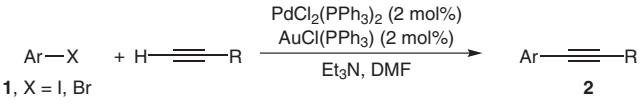
Entry	ArX	Temp (°C)	Time (h)	Product	Yield[b] (%)
13	 **1k**	90	9	 **2l**	90 (27)[d]
14	 **1l**	90	9	 **2m**	93 (29)[d]
15	 **1m**	80	3	 **2n**	92[e,f]
16	 **1n**	80	3	 **2o**	91
17	 **1o**	80	4	 **2p**	91
18	 **1o**	80	4	 **2q**	89
19	 **1p**	90	6	 **2d**	86
20	 **1q**	80	4	 **2r**	62 (0)[d]
21	 **1r**	80	4	 **2s**	60 (0)[d]
22	 **1b**	80	5	 **2t**	72 (0)[d,g]

Table 2 Sonogashira Coupling of Aryl or Heteroaryl Iodides and Bromides with Terminal Alkynes[a] (continued)



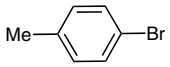
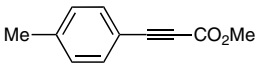
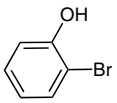
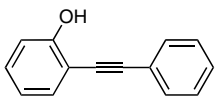
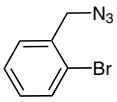
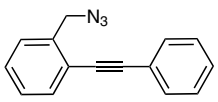
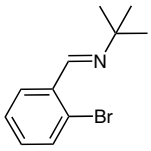
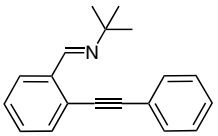
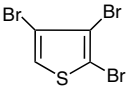
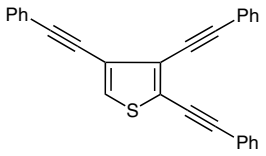
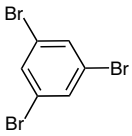
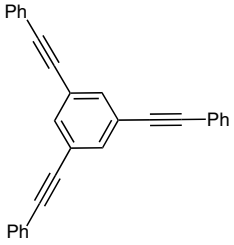
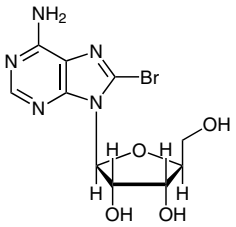
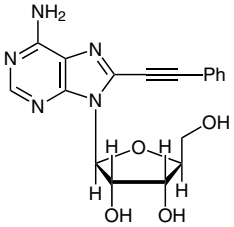
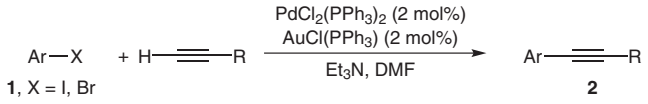
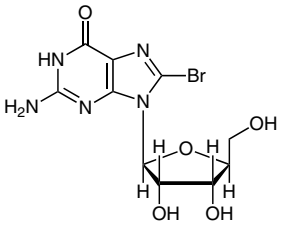
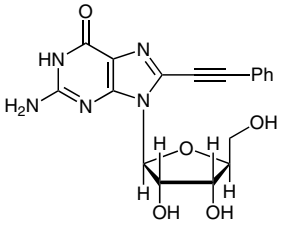
Entry	ArX	Temp (°C)	Time (h)	Product	Yield[b] (%)
23	 **1g**	80	5	 **2u**	70 (0)[d,g,h]
24	 **1s**	80	3	 **2v**	92 (0)[d]
25	 **1t**	80	3	 **2w**	92
26	 **1u**	80	3	 **2x**	90
27	 **1v**	90	12	 **2y**	84[i]
28	 **1w**	100	10	 **2z**	94[i]
29	 **1x**	90	5	 **2aa**	83[j]

Table 2 Sonogashira Coupling of Aryl or Heteroaryl Iodides and Bromides with Terminal Alkynes[a] (continued)



Entry	ArX	Temp (°C)	Time (h)	Product	Yield[b] (%)
30	 **1y**	90	5	 **2ab**	88[j]

[a] Reaction conditions: aryl halide (1 mmol), acetylene (1.1 mmol), Et_3N (3 mmol), DMF (3 mL).
[b] Isolated yield.
[c] In the absence of a gold catalyst, 2 mol% $PdCl_2(PPh_3)_2$ gave the product in 18% yield after 3 h.
[d] Yield in parentheses refers to the product obtained using CuI in place of $AuCl(PPh_3)$.
[e] Replacement of $AuCl(PPh_3)$ by (IPr)AuCl gives the product in 94% yield in 1.5 h.
[f] 1 mol% $PdCl_2(PPh_3)_2$/1 mol% $AuCl(PPh_3)$ and a reaction time of 5 h gave the product in 89% yield.
[g] Cs_2CO_3 was used instead of Et_3N.
[h] 60% of the coupled product was isolated when K_2CO_3 was used as the base.
[i] Phenylacetylene (3.6 equiv) and Et_3N (9 equiv) were used.
[j] Workup procedure different from others, see the experimental section.

A pyridine nucleus containing more than one chlorine atom also coupled nicely under our reaction conditions. Thus, 2,6-dichloropyridine-3-carbaldehyde (**3d**) gives the corresponding dialkynylated product **4f** on reaction with 2.2 equivalents of phenylacetylene (Table 3, entry 6). Additionally, the dichloro aza-phthalide **3e** (entry 7) is also amenable to this methodology giving the desired dialkynylated aza-phthalide **4g** in high yield.

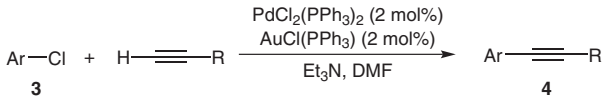
Electron-deficient aryl chloride 1-chloro-4-nitrobenzene (**3f**) couples with phenylacetylene and 4-(dimethylamino)phenylacetylene to give 71% and 64% of the coupled products **4h** and **4i**, respectively (Table 3, entries 8 and 9). Also, an electroneutral aryl chloride such as chlorobenzene (**3g**) couples with phenylacetylene to give 62% of the coupled product **2b** (entry 10). Furthermore, electron-rich aryl chloride 4-chlorotoluene (**3h**) reacts with phenylacetylene to afford the desired coupled product **2g** in moderate yield (entry 11). On the other hand, sterically hindered aryl chloride 1-chloro-2,6-dimethylbenzene (**3i**) couples with phenylacetylene to give the desired product **2d**, albeit in low yield (entry 12). Unfortunately, highly electron-rich 4-chloroanisole (**3j**) does not couple with phenylacetylene under these catalytic conditions (entry 13). This may be due to inability of palladium(0), generated from the precatalyst $PdCl_2(PPh_3)_2$, to undergo oxidative addition to the electron-rich C–Cl bond. Interestingly, addition of 20 mol% of potassium iodide in the catalytic ensemble in entries 11 and 12 reduces the reaction time and increases the yield from 52% to 64% and 41% to 56%, respectively (domino HALEX and Sonogashira reaction[21]).

We have also tested our method with highly reactive coupling partners e.g. a vinyl bromide. As can be seen from Table 4, entry 1, β-bromostyrene (**5**) couples with homopropargyl alcohol efficiently and furnishes the coupled product **6** in excellent yield. An acyl chloride also couples satisfactorily with a terminal alkyne (entry 2). Our method also proves to be effective for the Sonogashira coupling of aryl triflates with terminal alkynes; aryl triflate **9** bearing a sensitive acetonide moiety couples with phenylacetylene to furnish the desired coupled product **10** in 81% isolated yield (entry 3).[22]

As previously noted by Laguna and co-workers.[10] no trace of Glaser-type homocoupling of alkynes could be observed (TLC) in any of the reactions described in Tables 2–4, which were essentially clean. Furthermore, independent experiments were carried out to examine the role of palladium and gold separately in these reactions. While the gold complex $AuCl(PPh_3)$ was found to be totally inactive in the absence of the palladium complex $PdCl_2(PPh_3)_2$, the latter alone led to the formation of the coupled product (Table 2, entry 6) in 18% yield. Pd–Au dual catalytic reactions are also possible with lower catalytic loadings, although longer reaction times are needed for efficient conversions. For example, using 1 mol% $Pd(PPh_3)_2Cl_2$/1 mol% $AuCl(PPh_3)$ gave the product **2n** in 89% isolated yield after a reaction time of five hours (Table 2, entry 15). Incidentally, the assumption made by Laguna and co-workers[10] to explain the inactivity of $AuCl(PPh_3)$ in terms of the lesser propensity for the dissociation of the phosphine ligand seems untenable in view of our observation that replacement of the phosphine li-

gand by strongly bonded N-heterocyclic carbene ligand (IPr NHC) still gives the product **2n** (Table 2, entry 15) 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.[23] We have also compared the results of the Sonogashira coupling in the presence of the Pd–Au dual catalytic system with those obtained under classical conditions, that is, in the presence of copper(I) iodide and an amine [under identical conditions to those in Table 2 but replacing $AuCl(PPh_3)$ by CuI]. In these cases in Table 2 (entries 10, 13, 14, and 20–24) and Table 3 (entry 6) yields as given in parentheses are woefully low, the predominant byproduct being the Glaser-type homocoupling product (31–44%).

Table 3 Coupling of Aryl or Heteroaryl Chlorides with Terminal Alkynes[a]



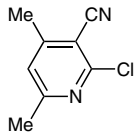
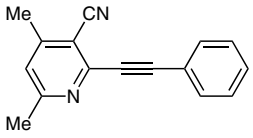
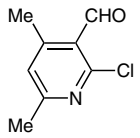
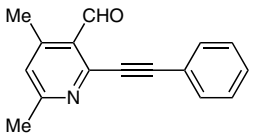
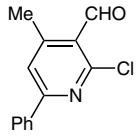
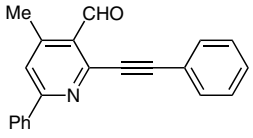
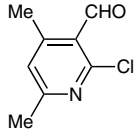
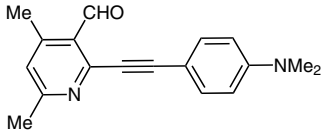
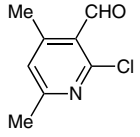
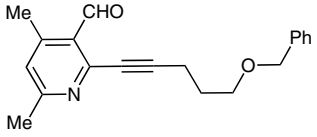
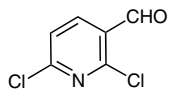
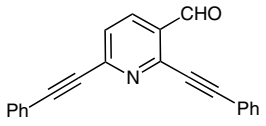
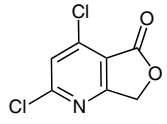
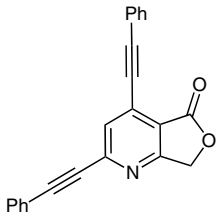
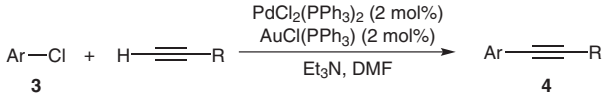
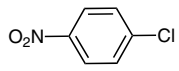
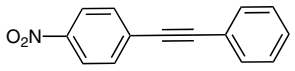
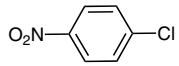
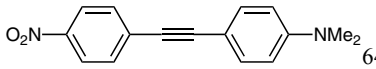
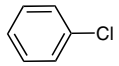
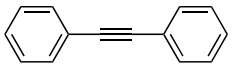
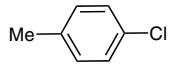
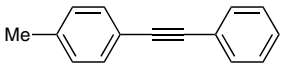
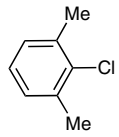
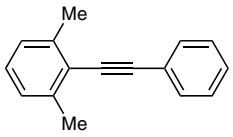
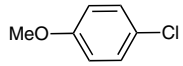
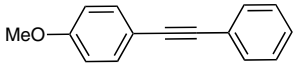
Entry	ArCl	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	 **3a**	80	3	 **4a**	94
2	 **3b**	80	3	 **4b**	91
3	 **3c**	80	3	 **4c**	94
4	 **3b**	80	3	 **4d**	86
5	 **3b**	80	3	 **4e**	90
6	 **3d**	90	6	 **4f**	81 (56)[c,d]
7	 **3e**	90	6	 **4g**	86[d]

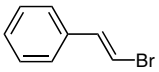
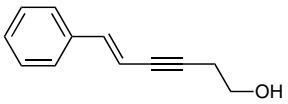
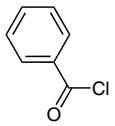
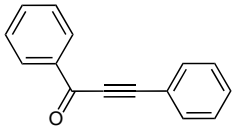
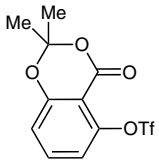
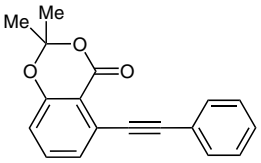
Table 3 Coupling of Aryl or Heteroaryl Chlorides with Terminal Alkynes[a] (continued)



Entry	ArCl	Temp (°C)	Time (h)	Product	Yield[b] (%)
8	 **3f**	100	6	 **4h**	71
9	 **3f**	100	6	 **4i**	64
10	 **3g**	100	12	 **2b**	62
11	 **3h**	120	12 (8)	 **2g**	52 (64)[e]
12	 **3i**	120	24(16)	 **2d**	41 (56)[e]
13	 **3j**	120	12	 **2k**	–

[a] Reaction conditions: aryl or heteroaryl chloride (1 mmol), acetylene (1.1 mmol), Et_3N (3 mmol), DMF (3 mL).
[b] Isolated yield.
[c] Yield in the parenthesis refers to the product obtained using classical $PdCl_2(PPh_3)_2$/CuI catalytic systems.
[d] Phenylacetylene (2.2 equiv) and Et_3N (6 equiv) were used.
[e] Yield and time in parentheses refer to those obtained using KI (20 mol%) as an additive.

Table 4 Coupling of Aryl Halide Surrogates with Alkynes[a]

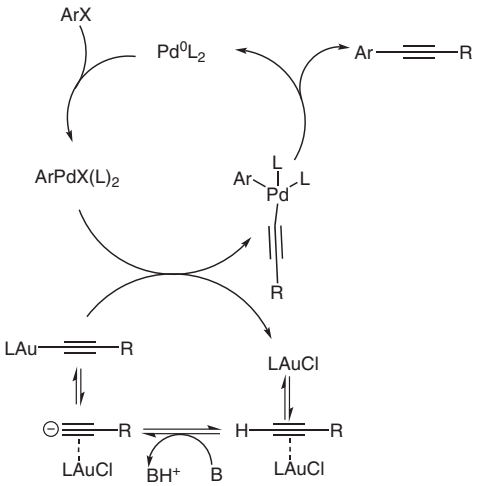
Entry	ArX	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	 **5**	r.t.	1	 **6**	96
2	 **7**	80	3	 **8**	76
3	 **9**	80	4	 **10**	81

[a] Reaction conditions: vinyl bromide, acyl chloride, or aryl triflate (1 mmol), acetylene (1.1 mmol), Et_3N (3 mmol), DMF (3 mL).
[b] Isolated yield.

A generally accepted mechanism of the classical Pd–Cu-catalyzed Sonogashira coupling consists of two catalytic cycles: (a) the classic palladium-based coupling reaction that involves the oxidative addition of an aryl halide ArX to a low coordinate palladium(0) complex, then transmetalation of a copper acetylide (formed in the second catalytic cycle) to generate an $ArPd(–C{\equiv}CR_2)L_2$ species, which subsequently undergoes *cis–trans* isomerization and reductive elimination to give the arylalkyne and the regenerated catalyst, and (b) the so-called 'copper cycle' in which the copper acetylide is generated from the free alkyne in the presence of a base, which is often an amine. The latter cycle is poorly understood; for example, the in situ formation of a copper acetylide is not proven yet, although recently indirect evidence has been found.[24] In fact, most of the amines used are not basic sufficiently to deprotonate the alkyne to provide an anionic species that can further react to give the corresponding copper acetylide. Therefore, a π-alkyne–Cu complex, which makes the alkyne proton more acidic is often proposed as an intermediate.[3]

For a better understanding of these reactions and other gold-catalyzed reactions, we embarked on mechanistic studies and attempted to characterize some intermediates. As already mentioned the gold-only procedure did not furnish any trace of the coupled product (Table 2, entry 6) thus proving the ineffectiveness of gold(I) for the oxidative addition to aryl halides. In light of the Pd–Ag catalytic alkynylation reaction reported by Pale et al.,[25] we have also investigated our Pd–Au dual catalytic reaction based on the similarities between gold and silver. On the basis of what is known and what we learned[12] from gold and alkyne interactions, the steps depicted in Scheme 2 may be proposed.

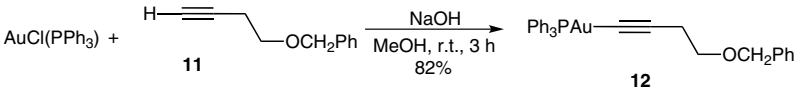
Coordination of alkynes to gold is well known; such coordination activates the alkyne toward nucleophilic addition or deprotonation. In the latter case a zwitterion should be formed, but it would rapidly rearrange to the more stable gold acetylide. Once formed, gold acetylides are known to enter into the palladium catalytic cycle at the transmetalation step[26] like other organometallics do. To check this assumption, we prepared the gold acetylide **12**[27] by treatment of a mixture of alkyne **11** and $AuCl(PPh_3)$ in methanol with methanolic sodium hydroxide solution at room temperature (Scheme 3) and it was characterized by ^1H, ^{31}P NMR as well as mass spectral analysis.



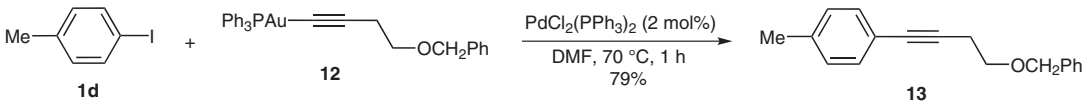
Scheme 2 Possible mechanism of Pd–Au dual catalytic Sonogashira coupling

The use of this gold acetylide **12** did not allow coupling with 4-iodotoluene (**1d**) whatever the conditions used; however, in the presence of a catalytic amount of $PdCl_2(PPh_3)$ it underwent a smooth transformation giving the expected coupled product **13** in good yield (Scheme 4).[28]

In conclusion, we have demonstrated that the reportedly inactive dual catalytic system $PdCl_2(PPh_3)_2/AuCl(PPh_3)$ allows efficient Sonogashira coupling of various aryl and heteroaryl halides. We have also shown the utility of our Pd–Au dual catalytic alkynylation method for various aryl halides that are known to be problematic in classical Pd–Cu Sonogashira coupling. In addition, other coupling partners, such as triflates, acyl halides, and vinyl halides are also amenable to this protocol. A key feature of the Pd–Au dual catalytic process is its extreme functional group tolerance. We have also worked out a thorough mechanistic rationale of the alkynylation process with a preformed gold acetylide. Further work for alkynylation of aryl chlorides at room temperature and expanding the scope of gold organometallics in coupling reactions is underway in our laboratory.



Scheme 3 Preparation of gold acetylide **12**



Scheme 4 Sonogashira coupling using preformed gold acetylide **12**

General details of the experiments are given in the Supporting Information. Petroleum ether = PE. TLC used detection by UV and I_2. (IPr)AuCl = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene-gold(I) chloride.

1-[4-(Phenylethynyl)phenyl]ethanone (2a); Typical Procedure under Laguna's Conditions[10]

4-Iodoacetophenone (**1a**, 369 mg, 1.5 mmol), phenylacetylene (0.25 mL, 2.25 mmol), and *i*-Pr_2NH (0.33 mL, 2.25 mmol) were stirred in THF (3 mL) under argon. $PdCl_2(PPh_3)_2$ (10.5 mg, 0.015 mmol) was added and the mixture was stirred for 10 min before the addition of [$AuCl(PPh_3)$] (7 mg, 0.015 mmol). The mixture was stirred at r.t. for 14 h, then it was diluted with Et_2O (5 mL), and filtered through a small Celite bed. The filtrate was poured into H_2O and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4), and the solvent was evaporated under reduced pressure. The product **2a** was isolated by column chromatography (silica gel); yield: 0.304 g (92%); also isolated was 4-iodoacetophenone; yield: 0.017 g (4%).

Pd–Au Dual Catalytic Sonogashira Coupling; General Procedure

A flame-dried two-necked flask, equipped with a reflux condenser, gas inlet/outlet, and rubber septum, was evacuated and backfilled with argon (2 ×) and then charged under a positive pressure of argon with the aryl or heteroaryl halide (1 mmol), DMF (3 mL), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and base (3 mmol), followed by $AuCl(PPh_3)$ (10 mg, 0.02 mmol) and a terminal acetylene (1.1 mmol). Then the mixture was heated at given temperature and time. It was diluted by Et_2O (3 mL) and filtered through a small Celite bed. The filtrate was poured into H_2O and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4) and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography (silica gel).

Pd–Au Dual Catalytic Sonogashira Coupling with Propiolates; General Procedure

A flame-dried two-necked flask, equipped with a reflux condenser, gas inlet/outlet, and rubber septum, was evacuated and backfilled with argon (2 ×) and then charged under a positive pressure of argon with the aryl or heteroaryl halide (1 mmol), DMF (3 mL), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and Cs_2CO_3 (3 mmol), followed by $AuCl(PPh_3)$ (10 mg, 0.02 mmol) and propiolate (1.1 mmol). Then the mixture was heated at the given temperature and time. It was diluted by Et_2O (3 mL) and filtered through a small Celite bed. The filtrate was poured into H_2O and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4) and the solvent was evaporated under reduced pressure. The product was isolated by column chromatography (silica gel).

Pd–Au Dual Catalytic Sonogashira-Type Cross-Coupling of 8-Bromoguanosine (1x) or 8-Bromoadenosine (1y); General Procedure

A flame-dried two-necked flask, equipped with a reflux condenser, gas inlet/outlet, and rubber septum, was evacuated and backfilled with argon (2 ×) and then charged under a positive pressure of argon with 8-bromoguanosine (**1x**)[17] or 8-bromoadenosine (**1y**)[17] (0.28 mmol, 1 equiv), DMF (4 mL), $PdCl_2(PPh_3)_2$ (4 mg, 0.0056 mmol), and Et_3N (3 equiv), followed by $AuCl(PPh_3)$ (3 mg, 0.006 mmol) and a terminal acetylene (0.34 mmol, 1.2 equiv). Then the mixture was heated at 90 °C for 5 h. After that it was allowed to cool to r.t. and diluted with Et_2O (30 mL). The solid precipitate was transferred to a sintered glass filter and was washed with boiling H_2O (3 × 10 mL), EtOAc (3 × 15 mL), and Et_2O (2 × 15 mL) yielding the coupled products. Spectral data of both the coupled products were matched with reported[17] values.

Preparation of Gold–Acetylide Complex 12

A soln of NaOH (15 mg, 0.375 mmol) in MeOH (2 mL) was added to the mixture of $AuCl(PPh_3)$ (77 mg, 0.15 mmol) and **11** (50 mg, 0.31 mmol) in anhyd MeOH (6 mL). Then the flask was covered by black paper and the mixture was allowed to stir at r.t. under argon for 3 h. The solvent was removed under reduced pressure. Then the crude product was diluted by Et_2O and filtered through a small Celite bed (to remove the salts) and the filtrate was dried in vacuo. The solid material was washed by anhyd hexane (2 × 4 mL) (to remove the excess **11**) and the solid was dried under vacuum; yield: 0.076 g (82%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.57–7.01 (m, 20 H), 4.54 (s, 2 H), 3.67 (t, *J* = 7.6 Hz, 2 H), 2.70 (t, *J* = 7.6 Hz, 2 H).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 46.15.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{29}H_{26}AuNaOP$: 641.1284; found: 641.1306.

4,6-Dimethyl-2-(phenylethynyl)pyridine-3-carbonitrile (4a)

From **3a** (0.17 g); light brown solid; yield: 0.22 g (94%); mp 84–86 °C; R_f = 0.34 (10% EtOAc–PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.67 (m, 2 H), 7.42–7.38 (m, 3 H), 7.08 (s, 1 H), 2.61 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2,151.2, 145.7, 132.5, 129.8, 128.5, 123.3, 121.3, 115.7, 110.9, 95.0, 86.1, 24.8, 20.3.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{16}H_{13}N_2$: 233.1073; found: 233.1074.

4,6-Dimethyl-2-(phenylethynyl)pyridine-3-carbaldehyde (4b)

From **3b** (0.17 g); light brown solid; yield: 0.214 g (91%); mp 79–81 °C; R_f = 0.26 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 7.60–7.56 (m, 2 H), 7.35–7.26 (m, 3 H), 6.98 (s, 1 H), 2.57 (s, 3 H), 2.56 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.2, 163.1, 149.9, 147.8, 132.3, 129.8, 128.7, 128.7, 126.4, 121.8, 95.7, 85.8, 24.9, 21.0.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{16}H_{14}NO$: 236.1070; found: 236.1075.

4-Methyl-6-phenyl-2-(phenylethynyl)pyridine-3-carbaldehyde (4c)

From **3c** (0.23 g); light brown solid; yield: 0.28 g (94%); mp 115–117 °C; R_f = 0.41 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.89 (s, 1 H), 8.12–8.07 (m, 2 H), 7.68–7.63 (m, 2 H), 7.57 (s, 1 H), 7.53–7.48 (m, 3 H), 7.42–7.37 (m, 3 H), 2.71 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.3, 160.4, 150.4, 148.2, 137.7, 132.3, 130.5, 129.8, 129.2, 129.0, 128.7, 127.8, 123.2, 121.8, 95.6, 86.1, 21.5.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{21}H_{16}NO$: 298.1232; found: 298.1238.

2-[4-(Dimethylamino)phenylethynyl]-4,6-dimethylpyridine-3-carbaldehyde (4d)

From **3b** (0.17 g); yellow solid; yield: 0.24 g (86%); mp 132–134 °C; R_f = 0.20 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 6.90 (s, 1 H), 6.60 (d, *J* = 9.0 Hz, 2 H), 2.96 (s, 6 H), 2.55 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.7, 162.8, 151.0, 149.7, 148.6, 133.6, 127.8, 125.4, 111.7, 107.8, 98.2, 84.6, 40.1, 24.9, 21.0.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{18}H_{19}N_2O$: 279.1497; found: 279.1510.

2-[5-(Benzyloxy)pent-1-ynyl]-4,6-dimethylpyridine-3-carbaldehyde (4e)
From **3b** (0.17 g); colorless liquid; yield: 0.276 g (90%); R_f = 0.32 (10% EtOAc–PE)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.66 (s, 1 H), 7.35–7.26 (m, 5 H), 6.98 (s, 1 H), 4.52 (s, 2 H), 3.61 (t, *J* = 6.1 Hz, 2 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 2.58 (s, 3 H), 2.55 (s, 3 H), 1.96 (t, *J* = 6.5 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 193.3, 162.5, 149.4, 147.9, 138.3, 128.3, 127.5, 125.7, 97.1, 77.6, 72.9, 68.8, 28.4, 24.6, 20.9, 20.7, 16.5, 14.1.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{20}H_{22}NO_2$: 308.1651; found: 308.1645.

2,3,4-Tris(phenylethynyl)thiophene (2y)
From **1v** (0.323 g); white solid; yield: 0.323 g (84%); mp 146–148 °C; R_f = 0.62 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67–7.61 (m, 6 H), 7.47–7.44 (m, 9 H), 7.29 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.7, 131.8, 131.7, 129.3, 129.0, 128.8, 128.6, 128.4, 128.3, 127.1, 126.8, 123.6, 123.1, 122.7, 122.5, 98.6, 94.7, 93.8, 83.6, 82.1, 81.9.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{28}H_{17}S$: 385.1051; found: 385.1047.

2,6-Bis(phenylethynyl)pyridine-3-carbaldehyde (4f)
From **3d** (0.176 g); light brown solid; yield: 0.250 g (81%); mp 117–118 °C; R_f = 0.18 (5% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 10.66 (s, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 7.67–7.56 (m, 5 H), 7.45–7.38 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.4, 148.4, 146.6, 135.2, 132.6, 132.5, 130.5, 130.2, 130.0, 128.8, 128.7, 126.7, 121.7, 121.4, 96.6, 94.0, 88.4, 84.6.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{22}H_{14}NO$: 308.1075; found: 308.1077.

2,4-Bis(phenylethynyl)-7*H*-furo[3,4-*b*]pyridin-5-one (4g)
From **3e** (0.204 g); brown solid; yield: 0.288 g (86%); mp 152–154 °C; R_f = 0.17 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71–7.62 (m, 5 H), 7.43–7.41 (m, 6 H), 5.29 (s, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.7, 148.7, 132.9, 132.6, 131.9, 131.5, 130.5, 130.2, 129.6, 129.3, 128.8, 121.6, 121.4, 117.4, 103.9, 94.5, 87.9, 82.9, 69.7.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{23}H_{14}NO_2$: 336.1025; found: 336.1030.

CAS Registry Numbers of Known Compounds
2a [1942-31-0], **2b** [501-65-5], **2c** [16017-24-6], **2d** [180783-48-6], **2e** [35010-17-4], **2f** [10229-11-5], **2g** [3287-02-3], **2h** [31208-53-4], **2i** [41398-67-8], **2j** [37696-01-8], **2k** [7380-78-1], **2l** [78594-14-6], **2m** [335605-74-8], **2n** [29778-27-6], **2o** [116509-98-9], **2p** [10271-65-5], **2q** [1001920-52-0], **2r** [13141-38-3], **2s** [13141-44-1], **2t** [4891-38-7], **2u** [7515-16-4], **2v** [92151-73-0], **2w** [947395-59-7], **2x** [241813-23-0], **2z** [118688-56-5], **2aa** [85110-32-3], **2ab** [85110-38-9], **4h** [1942-30-9], **4i** [62197-66-4], **6** [122305-60-6], **8** [7338-94-5], **10** [164014-45-3], **13** [1207298-89-2].

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(28) Independent of each other, both the Hashmi group[29] and our group[12] showed that the transmetalation from organogold(I) compounds to palladium is a generally applicable methodology, and in this context the Hashmi group also showed that gold acetylide (both phosphine and NHC gold complexes)[29] can enter into the palladium catalytic cycle. Incidentally, Echavarren et al.[30] investigated the Pd–Au dual catalytic Sonogashira coupling thoroughly. They found that gold(I) cannot perform the Sonogashira coupling in the absence of a palladium source. This also supports our reported[12] results, as $AuCl(PPh_3)$ was found to be totally inactive in the absence of the palladium complex $PdCl_2(PPh_3)_2$. While the investigation by Echavarren et al. is interesting, they did not conduct the crucial ICP analysis of their catalyst, which would have shown that in the control experiments the other metal is not present.[31]
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