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### The decisive role of ligand metathesis in Au/Pd bimetallic catalysis<sup>†</sup>

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AuClL<sup>1</sup>/PdCl<sub>2</sub>L<sup>2</sup><sub>2</sub> cocatalyzed coupling of Ar<sup>1</sup>X and Ar<sup>2</sup>SnBu<sub>3</sub> is feasible for bulky Ar<sup>1</sup>, provided that at least one ligand on Pd is not strongly coordinating. This can be achieved *in situ* by Au/Pd ligand exchange if L<sup>1</sup> is weakly coordinating. When the exchange is slow, independent preparation of appropriate catalysts is recommended.

Bimetallic catalysis is providing new powerful alternatives to the classic catalytic processes with only one transition metal as catalyst.<sup>1</sup> Many bimetallic processes are based on Au/Pd cocatalysis.<sup>2</sup> In recent work we uncovered the ability of AsPh<sub>3</sub> gold complexes to cocatalyze Stille reactions involving bulky aryls. The gold co-catalyst circumvents the formation of an overcrowded high energy Sn/Pd transition state that prevents or severely slows down the classic Stille reaction, by forming less hindered Au intermediates which, eventually, transmetalate the bulky aryl group to Pd (Scheme 1) through less hindered Sn/Au and Au/Pd transition states.<sup>3</sup> In that experimental and DFT mechanistic study, AsPh3 was utilized as a ligand for the two metals, in order to skip possible observational complications arising from scrambling of the ancillary ligands.<sup>4</sup> The reaction also worked with PPh<sub>3</sub>, but much more slowly due to the fact that transmetalations on Pd are slower for phosphine than for arsine complexes.<sup>5</sup> Transfer under cocatalytic conditions of PPh<sub>3</sub> from Au to Pd (by HRMS) and from Pd(PPh<sub>3</sub>)<sub>4</sub> to Au to form catalytically less active [(PPh<sub>3</sub>)<sub>2</sub>Au]<sup>+</sup> (by NMR) has been observed before but it has never been studied comprehensively or carefully.1f



Scheme 1 Au/Pd co-catalyzed Stille reaction.

I. U. CINQUIMA/Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47071 Valladolid, Spain. E-mail: espinet@qi.uva.es, casares@qi.uva.es † Electronic supplementary information (ESI) available: Experimental and synthetic characterization details; NMR experiments and data. See DOI: 10.1039/c3cc43133a Having established the basic framework of the mechanism of the Au-cocatalyzed Stille process, it is now possible to address the effect of changing the ancillary ligands (a typical strategy used in synthesis optimization) from a mechanistic point of view. This study uncovers aspects such as the thermodynamic preference of each metal for different ligands, the kinetics of ligand scrambling, and the importance of the several mechanistic steps in the process using three representative ancillary ligands, PPh<sub>3</sub>, AsPh<sub>3</sub>, and IDM (IDM = 1,3-dimethyl-imidazol-2-ylidene), and their combinations by pairs.

As in our previous work,<sup>3</sup> our study model is the coupling of p-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I (1) with the sterically demanding nucleophile MesSnBu<sub>3</sub> (2, Bu = *n*-butyl), catalyzed with  $[PdCl_2L^1L_2^2]$  and  $[AuClL^3]$  (L<sup>1</sup>, L<sup>2</sup>, or L<sup>3</sup> = AsPh<sub>3</sub>, PPh<sub>3</sub>, or IDM). This coupling works only in the presence of gold co-catalysts. AsPh<sub>3</sub> and LiCl were added in all of the mechanistic tests, in order to keep the reaction conditions constant. The experimental kinetic conditions were Pd:Au:Cl:As<sub>added</sub> = 1:1:saturated:2, where Pd and Au stand for the Pd and Au catalyst used, with the corresponding ligand in each case (Scheme 2).

The initial catalytic tests using combinations of metal complexes with different ligands revealed that in the final mixture the complexes did not always correspond to the initial ones. Sometimes ligand rearrangement occurred during the catalytic process, and the scrambling rate could be fast or slow. This scrambling had to be studied separately, stoichiometrically, in order to understand the catalytic performance. The ligand exchange processes observed stoichiometrically are shown in Scheme 3 (see Table 1 for ligand labels).

For instance, the stoichiometric reaction between  $[PdCl_2(IDM)_2]$ (6) and  $[AuCl(AsPh_3)]$  (12) (Scheme 3a) leads to [AuCl(IDM)] (10) and the mixed palladium complex  $[PdCl_2(IDM)(AsPh_3)]$  (9). Thus, Pd transfers half of the IDM ligand available in exchange for AsPh<sub>3</sub>. However, starting from  $[PdCl_2(AsPh_3)_2]$  (8) and [AuCl(IDM)]



Scheme 2 Summary of experiments

a)	[PdCl <sub>2</sub> (IDM) <sub>2</sub> ] ( <b>6</b> ) + [AuCl(AsPh <sub>3</sub> )] ( <b>12</b> )	[PdCl <sub>2</sub> (IDM)(AsPh <sub>3</sub> )] (9) + [AuCl(IDM)] ( <b>10</b> )			
b)	[PdCl <sub>2</sub> (AsPh <sub>3</sub> ) <sub>2</sub> ] ( <b>8</b> ) 24 h + [AuCl(IDM)] ( <b>10</b> )	[PdCl <sub>2</sub> (IDM)(AsPh <sub>3</sub> )] (9) + [AuCl(AsPh <sub>3</sub> )] ( <b>12</b> )			
c)	[PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> ] ( <b>7</b> ) + [AuCl(AsPh <sub>3</sub> )] ( <b>12</b> )	[AuCl(PPh <sub>3</sub> )] ( <b>11</b> ) + [PdCl <sub>2</sub> (PPh <sub>3</sub> )(AsPh <sub>3</sub> )] ( <b>13</b> )			
	$[PdCl_2(PPh_3)_2]$ (7) + $[PdCl_2(AsPh_3)_2]$ (8)				
d)	$[PdCl_2(AsPh_3)_2]$ (8) + $[AuCl(PPh_3)]$ (11) $\xrightarrow{24 h} \times$				
Scheme 3	Ligand scrambling processes.				

(10) (Scheme 3b), an equilibrium is reached by partial transfer of the IDM ligand from Au to Pd. These equations show how delicate the thermodynamic balance is for these systems, but also suggests that, in the equilibrium, a Pd with two strongly coordinating ligands will be prone to transfer one to gold if the starting Au complex has a more weakly coordinating ligand. Monitoring of this ligand exchange shows that it takes about 24 h at 80  $^{\circ}$ C (the temperature used in the catalytic process) for completion of the ligand rearrangement (see Fig. S1 in ESI<sup>†</sup>). Thus, this rearrangement is unexpectedly slow, with a rate comparable to the catalytic process. It is worth warning that it may be frequent that, in similar cases, the actual catalytic systems will contain mixtures of catalytic species changing along the catalysis.

The PPh<sub>3</sub>/AsPh<sub>3</sub> metathesis is much faster than the IDM/AsPh<sub>3</sub> exchange, but shows further complications. The reaction of [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] (7) with [AuCl(AsPh<sub>3</sub>)] (12) (Scheme 3c) is complete after five minutes at 80  $^{\circ}C_{1}^{6}$  leading to the formation of [AuCl(PPh<sub>3</sub>)] (11) and [PdCl<sub>2</sub>(PPh<sub>3</sub>)(AsPh<sub>3</sub>)] (13) (again, Au takes one strongly coordinating ligand from Pd), but 13 disproportionates in part to  $[PdCl_2(PPh_3)_2]$  (7) and  $[PdCl_2(AsPh_3)_2]$  (8). While using acetonitrile as the reaction solvent, the gold complex [AuCl(PPh<sub>3</sub>)] (12) is observed by <sup>31</sup>P NMR, but fast ligand/solvent exchange in palladium complexes precludes the observation of the individual Pd complexes. Yet our assignment is supported by the following observations: (i) evaporation of the acetonitrile and dissolution in CDCl<sub>3</sub> (where ligand-solvent exchange does not occur) allow for the observation of  $[PdCl_2(PPh_3)_2]$  (7) and  $[PdCl_2(PPh_3)(AsPh_3)]$  (13); (ii) the same problem in observation by <sup>31</sup>P NMR is found with an equimolar mixture of [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>] and [PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>] in acetonitrile; and (iii) the reaction of  $[PdCl_2(PPh_3)_2]$  (7) with  $[AuCl(AsPh_3)]$  (12) in tetrachloroethane-d<sub>2</sub> at 80 °C also gives [AuCl(PPh<sub>3</sub>)] (11) and a mixture of  $[PdCl_2(PPh_3)(AsPh_3)]$  (13),  $[PdCl_2(PPh_3)_2]$  (7), and  $[PdCl_2(AsPh_3)_2]$  (8). Finally, no reaction is observed when [AuCl(PPh<sub>3</sub>)] (11) and [PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>] (8) are mixed in acetonitrile, showing the very high preference of gold for PPh<sub>3</sub> (Scheme 3d).

Considering the previous results, not only homogeneous but also mixed-ligand complexes were tested as catalysts. The results of all cross-coupling catalytic experiments are gathered in Table 1. Entries 1–3 show the results of reactions with the same ligand on both metals.<sup>7</sup> In each of these three entries the possible occurrence of ligand scrambling is, expectedly, kinetically irrelevant since it does not produce chemical changes in the catalysts. We find that the carbene ligand totally blocks the Au/Pd catalyzed coupling (entry 1).

**Table 1** Pd/Au co-catalyzed cross-coupling reaction of p-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I (1) with MesSnBu<sub>3</sub> to give p-Mes-C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> (3), with different ligands in the initial gold and palladium cocatalysts, as shown in Scheme 2 above

Entry	L <sup>1</sup> , L <sup>2</sup> (Pd cat.)	L <sup>3</sup> (Au cat.)	<b>3</b> <sup>f</sup> (%) (24 h)	Final conversion <sup>g</sup> 3:4:5:1:other % ratio (hours)
$1^a$	2IDM (6)	IDM (10)	0	0:0:0:0(48)
$2^a$	$2PPh_3(7)$	$PPh_3(11)$	14	$96:3:1:0(310)^{b}$
3 <sup><i>a</i></sup>	$2AsPh_3(8)$	$AsPh_3(12)$	84	84:8:6:2 (24)
$4^a$	2IDM (6)	$AsPh_3$ (12)	44	$65:16:10:9(72)^{c}$
$5^a$	IDM, $AsPh_3$ (9)	IDM (10)	66	89:7:0:4 (48)
$6^a$	IDM, $AsPh_3$ (9)	$AsPh_3$ (12)	76	87:8:4:1 (48)
$7^a$	$2AsPh_3$ (8)	IDM (10)	78	90:10:0:0 (38)
8 <sup>a</sup>	$2PPh_3$ (7)	$AsPh_3$ (12)	59	96:3:1:0 (84)
9 <sup>a</sup>	$2AsPh_3$ (8)	$PPh_3$ (11)	43	$75:14:7:0(250)^{b}$
$10^d$	$2AsPh_3$ (8)	$AsPh_3$ (12)	40	53:26:13:3:5 (89)
11 <sup>d</sup>	IDM, $AsPh_3$ (9)	IDM (10)	37	81:15:0:0:4 (89)
$12^d$	IDM, $AsPh_3$ (9)	$AsPh_3$ (12)	60	81:15:0:0:4 (89)
13 <sup>d</sup>	$2AsPh_3$ (8)	IDM (10)	71	86:12:0:0:2 (89)
$14^d$	$2PPh_3$ (7)	$AsPh_3$ (12)	29	83:2:0:15:0 (89)
$15^e$	IDM, $AsPh_3$ (9)	IDM (10)	26	52:5:0:40:0 (115)
$16^e$	IDM, $AsPh_3$ (9)	$AsPh_3$ (12)	41	53:6:0:34:7 (115)
$17^e$	$2AsPh_3$ (8)	IDM (10)	28	39:2:0:34:1 (115)

<sup>*a*</sup> NMR tubes were charged with solutions containing solvent MeCN saturated with LiCl; temperature 80 °C; [*p*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I] = 0.10 M; [SnRBu<sub>3</sub>] = 0.11 M; [AsPh<sub>3</sub>] =  $4 \times 10^{-3}$  M. [Pd] =  $2 \times 10^{-3}$  M; [Au] =  $2 \times 10^{-3}$  M. The reactions were monitored until total conversion of the initial reagent or for the time indicated. Yields were determined by <sup>19</sup>F NMR integration and are average of two runs. <sup>*b*</sup> Taken from ref. 3. <sup>*c*</sup> Deposition of metal was observed. <sup>*d*</sup> No added AsPh<sub>3</sub>. <sup>*e*</sup> No added AsPh<sub>3</sub> and no LiCl. <sup>*f*</sup> Percentage of 3 formed in 24 h. <sup>*g*</sup> Final conversion is the conversion achieved up to the moment when the last measurement is taken (hours), and is the difference to 100 of the percentage of unreacted 1 (*e.g.* 94% in entry 3).

PPh<sub>3</sub> gives only slow reaction rates (entry 2) compared to AsPh<sub>3</sub> (entry 3), which gives the fastest reaction. These results are easily understood in view of our recent mechanistic study:3 since the transmetalation to Pd (whether associative or dissociative) implies release of one ligand from the palladium catalyst,<sup>8</sup> the R<sup>1</sup> (Au-to-Pd) transmetalation step (Scheme 1) is rate determining when the ligand to be displaced is a strongly coordinating one. Consistently, very good donors such as IDM block efficiently the catalysis at that point; the slightly weaker donor PPh3 produces slow transmetalation (14% in 24 h); and the more weakly coordinating ligand AsPh<sub>3</sub> gives the fastest transmetalation (84% in 24 h). Although AsPh<sub>3</sub> is faster, the highest yield after total conversion, and the highest selectivity to 3, is found for PPh<sub>3</sub>, but only after 310 h (entry 3). We have shown before that homocoupling products such as 4 are formed from undesired  $R^{1}/R^{2}$  transmetalations,<sup>9</sup> and these seem to be more disfavoured with PPh3, as compared to AsPh3.

The formation of mixed-ligand palladium complexes (Scheme 3) explains the catalytic activity observed for the other systems in Table 1. Thus, entries 4 and 5 are closely related because the initial system in entry 4 must be slowly evolving to the initial system used in entry 5 as the reaction progresses. Initially, the reaction in entry 4 is inefficient because complex **6** is blocking the process. Only when **9** starts to exist the transmetalation and coupling can complete the second catalytic cycle, and the reaction runs at a progressively increasing rate as the concentration of active **9** increases to its equilibrium value. One AsPh<sub>3</sub> ligand in the palladium complex (as in **9**) is enough to provide a kinetically active coordination site (protected with an easily leaving ligand) that allows for the Au to Pd transmetalation and subsequent coupling reaction to occur. The slowness of the ligand metathesis has

the undesired side effect observed in entry 4: since arylgold complexes are not thermally stable in solution at 80 °C, the [AuR<sup>1</sup>L] intermediates initially formed by Sn/Au transmetalation do not find a palladium complex suitable for transmetalation. For this reason, considerable decomposition of the gold catalyst is observed during the initial period of the reaction, which reduces the overall catalytic activity of the system and leads to lower yields and lower percentage of the crosscoupling product. The problem disappears when the Pd complex used from the beginning has one labile AsPh<sub>3</sub> ligand (entry 5).<sup>10</sup> Not much difference is made whether Au comes with an inert or a labile (entry 6) ligand because the ligand on Au is not dissociated during the process.<sup>11</sup> The rate and yields in the heterocoupling compound (3) of the catalysis can still be noticeably improved using two labile (and weak) ligands on Pd, which increase the electrophilicity of the Pd centre, and an inert (and strong) ligand on Au, which improves the stability of the gold intermediates (entry 7). In fact IDM seems to be the best stabilizer for gold, and the formation of the reduction product 5 is totally suppressed by the use of [AuCl(IDM)] (entries 5 and 7).<sup>12</sup>

For entry 8 we expect, as in entry 4, ligand rearrangement (fast in this case) to produce [AuCl(PPh<sub>3</sub>)]. Thus the gold intermediates are fairly well stabilized and decomposition *via* hydrolysis is almost absent. As shown in eqn (c) of Scheme 3, part of the palladium catalyst remains sequestered in the kinetically slow form, which is detrimental to the overall catalytic rate of the system. In spite of that, this combination turns out to be as selective as entry 2, with the best cross-coupling selectivity, and four times faster, providing probably the most convenient catalytic system.

Somehow to our surprise the catalyst combination in entry 9 makes a bad system, showing bad selectivity to **3**. Entries 9 and 4 have in common that noticeable reduction to metal is observed at the beginning and then the catalysis yields noticeable amounts of homocoupling and reduction products. It is not easy to understand in the case of entry 9 but the observation of metal deposition suggests that these combinations might be less protected against redox incompatibility,<sup>13</sup> perhaps in minor intermediates produced by ligand dissociation.

The best catalytic combinations were tested sparing the AsPh<sub>3</sub> stabilizing additive (entries 10–14). Then, those still working fine were tested without LiCl (entries 15–17). The results in Table 1 show that, for the selected reactions, the suppression of adding AsPh<sub>3</sub> produces an increase of homocoupling, but in the best combination ([PdCl<sub>2</sub>(AsPh<sub>3</sub>)<sub>2</sub>] + [AuCl(IDM)]) the suppression of added AsPh<sub>3</sub> has no cost. In all cases the suppression of LiCl is lethal and has a very detrimental effect on the conversion.<sup>14</sup>

In summary, although often ignored or overlooked, ligand metathesis is probably a frequently operating process in homogeneous catalysis, which can become decisive for the success of the reaction when different metals and ligands are involved in a bimetallic catalysis. Ligand exchange can be slow, with the consequence that the catalytic system is changing during the reaction. Use of the most stable ligand combination from the beginning, or preformed catalysts with mixed ligands, is advised for these cases, thus skipping their cumbersome or sluggish formation in solution and long preactivation times, and prevent undesired side reactions. However, if the ligand rearrangement is fast compared to the catalyzed reaction, as in entry 9, this precaution is not necessary. For the cases studied the ligand scrambling lead to catalysts with the best  $\sigma$ -donor ligand (IDM > PPh<sub>3</sub> > AsPh<sub>3</sub>) on the gold atom, which is very convenient since it produces a palladium complex with at least one labile ligand (AsPh<sub>3</sub>) and a gold complex coordinated with the best and more stabilizing ligand (IDM or PPh<sub>3</sub>). According to our previous study, the transmetalation step from Sn to Au is much easier than the Sn to Pd transmetalation and occurs without ligand dissociation. Hence, the coordination of the best ligand to gold has many advantages, improving its stability and minimizing the formation of hydrolysis products that might occur on gold.<sup>3</sup> On the other hand, the Au to Pd transmetalation to Pd is rate determining for strongly coordinating ligands, and having one weaker, easier to displace ligand in the coordination sphere of Pd strongly reduces the activation energy of this transmetalation, and increases the overall rate of the catalysis.<sup>15</sup> The combination of these two conditions leads to the best catalytic systems.

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