Transmetalation

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Strong Metallophilic Interactions in the Palladium Arylation by Gold Aryls**

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Bimetallic Au/Pd catalyzed C–C coupling is currently a very active research topic.[1–3] It requires R-group transmetalation from Au to Pd, but in spite of the extraordinary attention recently paid to these Au/Pd systems in synthesis, no mechanistic study of the Au/Pd R exchange has been reported. The first evidence of such Au/Pd transmetalation in a catalytic reaction was recognized, as a reversible process, in the gold-catalyzed *trans* to *cis* isomerization of [PdRf$_2$(tht)$_2$] complexes (Rf = 3,5-dichloro-2,4,6-trifluorophenyl; tht = tetrahydrothiophene), for which isomerization at the Pd center was proposed to occur through aryl transmetalation in a bimetallic Pd/Au intermediate supported by an Au–Pd bond.[4] Only very recently, Chen and co-workers studied, in the gas phase, in silico, and in solution, the related Au/Pt transmetalation of methyl groups, starting from *cis*-[PtMe$_2$(dmpe)] and [AuCl(PR$_3$)] (dmpe = bis(dimethylphosphino)ethane), using electrospray ionization techniques and a Cl$^-$ abstractor to create a cation in situ.[5,6] These experimental conditions depart from those used in Au/Pd systems for synthesis and catalysis, and the theoretical calculations on that Au/Pt system did not provide reasonable activation energy values, but interestingly the transmetalation intermediates proposed by Chen, although cationic due to the abstraction of Cl$^-$ that triggers the reaction, do show Au–Pt bonds. Herein we report an experimental study and DFT calculations of the Au/Pd aryl exchange on neutral catalytic reagents in common synthetic conditions. All experimental and calculation details are given in the Supporting Information.

Inspired by the microscopic reversibility principle, we chose *cis*-[Pd(C$_6$Cl$_2$F$_3$)$_2$(AsPh$_3$)$_2$] (**1**), because it is resistant to coupling and allows study of the transmetalation in the reverse sense of the usual coupling reaction. This approach has been used before in the study of the Stille reaction.[7] At 50 °C the reaction in Figure 1 was complete in less than 5 min, but the kinetic studies were carried out at −10 °C to make the reaction slower.

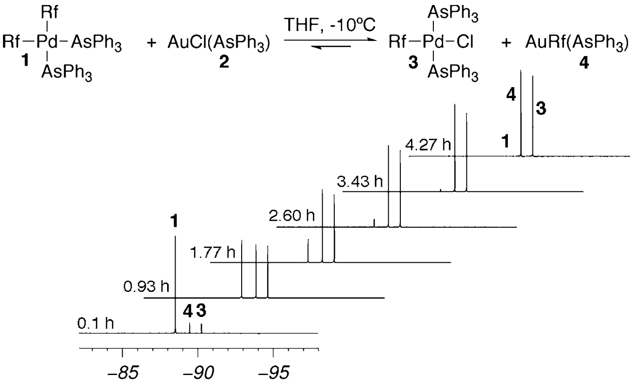

Figure 1. ^{19}F NMR spectroscopic monitoring at −10 °C of the Pd/Au transmetalation reaction **1** + **2** in 1:2 molar ratio (the excess of **2** does not react).

Interestingly, product **3** did not transmetalate further with an excess of **2** in solution, revealing that in this case [PdAr$_2$L$_2$] arylates [AuXL] (Figure 2a) but [PdArXL$_2$] does not (Figure 2b; Ar = aryl, X = halogen). This is probably a frequent thermodynamic profile, since PdAr$_2$ complexes must be stronger arylating agents than PdArX complexes. However, the reactions in Figure 2 are reversible, and, in a synthesis using gold aryls, the transmetalation [AuArL] + [PdArXL$_2$] will run counter-thermodynamically, provided [PdAr$_2$L$_2$]

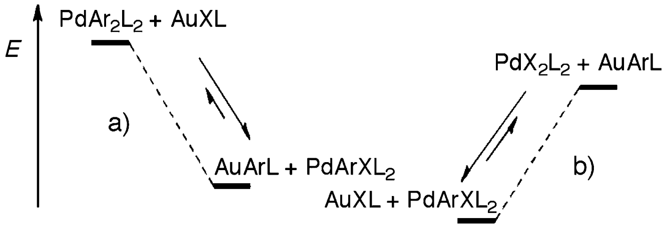

Figure 2. Qualitative thermodynamic balances for arylation exchange between gold Au^{I} and Pd^{II} complexes.

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undergoes C–C irreversible coupling making the overall process thermodynamically favorable.

Kinetic experiments followed by ^{19}F NMR spectroscopy afforded essential information. Very interestingly, addition of $AsPh_3$ slowed down the reaction (Table 1), and the observed reaction order with respect to the concentration of arsane, determined from initial rates (the slope of $\ln(r_0)$ vs. $\ln[AsPh_3]$), was −0.52. The overall reaction followed second-order kinetics in the two metal complexes (Figure 3).[8]

Table 1: Initial rates for the retro-transmetalation reaction between **1** and **2** in THF at −10 °C in the presence of added $AsPh_3$.[a]

$[AsPh_3]_{added}$ $[10^{-3}\ mol\,L^{-1}]$	r_0 $[10^{-6}\ mol\,L^{-1}\,s^{-1}]$
1.60	2.29 ± 0.10
3.00	1.80 ± 0.11
4.55	1.37 ± 0.05
6.25	1.13 ± 0.04

[a] Up to 20% conversion. $[1]_0 = 0.010\ mol\,L^{-1}$, $[2]_0 = 0.028\ mol\,L^{-1}$.

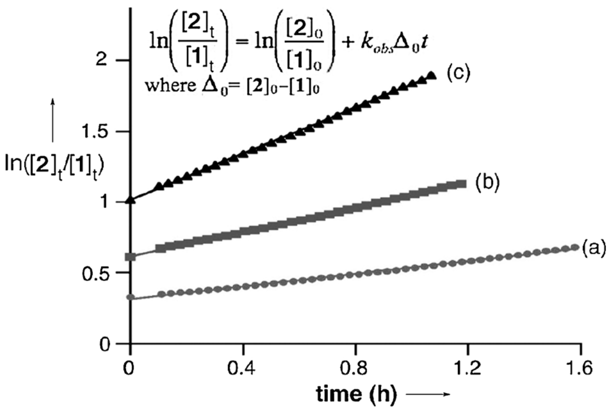
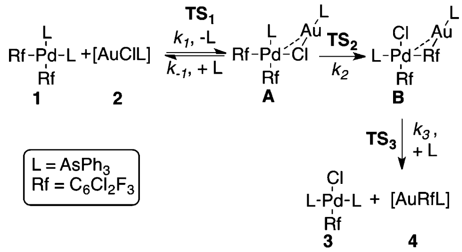


Figure 3. Plot of $\ln([2]_t/[1]_t)$ versus time: a) $[2]_0 = 0.014\ mol\,L^{-1}$; b) $[2]_0 = 0.019\ mol\,L^{-1}$; c) $[2]_0 = 0.028\ mol\,L^{-1}$. Starting conditions: $[1]_0 = 0.01$ M in THF at −10 °C.

The experimental kinetic data under various initial conditions were fitted to the initial multistep kinetic model proposed in Scheme 1, using nonlinear least-squares (NLLS) regression (for details, see the Supporting Information). Note that fitting the observed reaction order with respect to the concentration of arsane (−0.52) required the existence of two transition states, the second one having somewhat higher free energy than the first one. Moreover, the failure to observe any reaction intermediate by ^{19}F NMR imposes that the states containing **A** and **B** should have an energy at least 4 kcal mol^{-1} higher than the state containing the reagents. Kinetic simulations fulfilling these conditions showed that the reaction order on arsane concentration was dependent on the energy difference of the two transition states $\mathbf{TS_1}$ and $\mathbf{TS_2}$, and was essentially independent of the energy assumed for intermediate **A**. The best kinetic fitting was reached for $\mathbf{TS_1} = 17.7\ kcal\,mol^{-1}$ and $\mathbf{TS_2} = 20.6\ kcal\,mol^{-1}$ (see the Supporting Information).



Scheme 1. Kinetic model for the retro-transmetalation reaction.

With these experimental results in hand, we undertook a DFT theoretical study of the reaction. Since the energy of the kinetically relevant transition states is known from the experimental study, the DFT study was aimed mostly at providing the structures of transition states and intermediates. *cis*-$[PdPh_2(AsMe_3)_2]$[9] and $[AuPh(AsMe_3)]$ were used as the model complexes. It is worth noting that the experimental data are quite stringent for the calculations, since the latter should reasonably match not only one rate-determining state, but also the order of the energy of two transition barriers, which controls the arsane dependence observed experimentally.[10] The model chosen performed remarkably well.[11]

The results (Figure 4) account satisfactorily for the experimental results. They show that the calculated initial transition state corresponds to an associative ligand substitution by the entering gold complex **M2**, and leads to intermediate **I1**.[12] Then a higher energy transition state

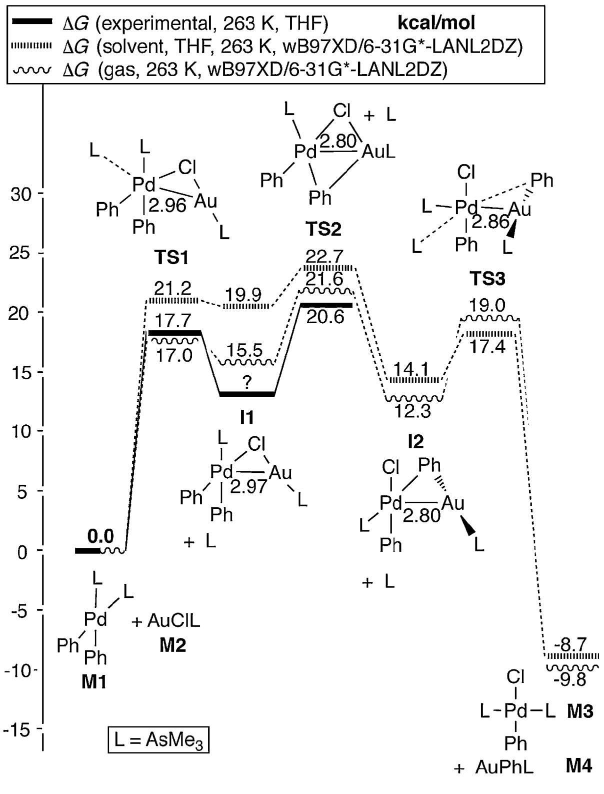


Figure 4. Profile of the exchange reaction **M1** + **M2** to give **M3** + **M4**, showing the experimental value for **TS1** and **TS2** in THF at −10 °C and the calculated values **TS1** and **TS2** in gas phase (wavy lines) and in THF solution (dashed lines). The Au–Pd distances (Å) in the calculated structures are shown.

TS2 follows, leading to **I2**, which rapidly yields the products by re-coordination of the displaced arsane.[13] In good agreement with the calculated ΔG^0 value for the transmetalation equilibrium $\mathbf{M1} + \mathbf{M2} = \mathbf{M3} + \mathbf{M4}$ ($\Delta G^0 = -8.6\,\mathrm{kcal\,mol^{-1}}$), the experimental transmetalation reaction is completely shifted to the right, as observed by ^{19}F NMR spectroscopy (Figure 1). This ΔG^0 value cannot be determined experimentally because the concentration of **1** in the final equilibrium is not detectable.

The free energy order of the theoretical transition states, **TS1** < **TS2**, is as required from the kinetic experimental studies, and intermediates **I1** and **I2** are sufficiently high in energy to be undetectable by NMR spectroscopy. The actual theoretical values in solvent are 3.5 (for **TS1**) and 2.1 (for **TS2**) $\mathrm{kcal\,mol^{-1}}$ higher than the corresponding values calculated from the experimental data. As for the energy separation between the two kinetically relevant transition states, the experimental difference $\mathbf{TS_2}-\mathbf{TS_1}$ is $2.9\,\mathrm{kcal\,mol^{-1}}$, and the DFT difference **TS2**−**TS1** is $1.5\,\mathrm{kcal\,mol^{-1}}$ in solvent and $4.6\,\mathrm{kcal\,mol^{-1}}$ in gas phase, both of which are close to 2.9.[14] These results are in line with the kinetic proposal.

The theoretical calculations provide details of the mechanistic profile and other very interesting features of the system. First of all, they show that the transition state with the highest energy in the transmetalation multistep process is **TS2**, which has a structure in which Au and Pd are exchanging X (Cl) for R (Ph) (Figure 5). This is in common with the Negishi and Stille processes studied before,[14,15] in which the Zn/Pd or Sn/Pd TS exchanging X (Cl) for R (Ph) is also the highest barrier in the multistep transmetalation.

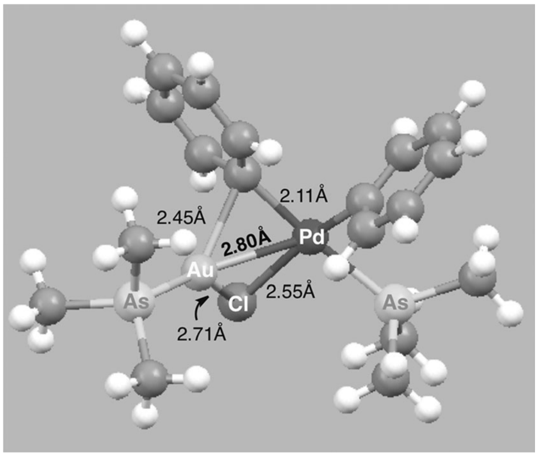


Figure 5. Calculated structure of **TS2**.

The calculated structures of **TS2** (Figure 5), **I1** (Figure 6), and the other intermediates and transition states (SI), are very informative. The Au−Pd distances in all the bimetallic species, shown in the reaction profile in Figure 4, are in the range 2.97–2.80 Å, which is much shorter than the sum of van der Waals radii of Au and Pd (3.29 Å) and very close to covalent bond distances (the sum of covalent radii is 2.75 Å). This indicates very strong metallophilic interactions, which are formed even if this requires elongation of other alternative bonds to make room for the metallophilic Au−Pd interaction. For example, the structure of intermediate **I1** might have been expected to be **I1a** (Figure 6), having Au and Pd simply connected by a bridging Cl ligand, with a Pd−Cl distance of about 2.3 Å,[16] and an Au−Cl distance of about 2.5 Å, at most.[17] Far from this naive prediction, the calculated intermediate (**I1**) shows a very large Pd−Cl distance (2.74 Å),[18] which seems to be a bonding compromise to make room for a metallophilic Au−Pd interaction at 2.97 Å. In fact, the whole transmetalation process pivots around these metallophilic interactions, which come close to the range of covalent Pd−Au bonds at the heart of the transmetalation (the Cl for Ph exchange step) in **TS2** (Figure 5).

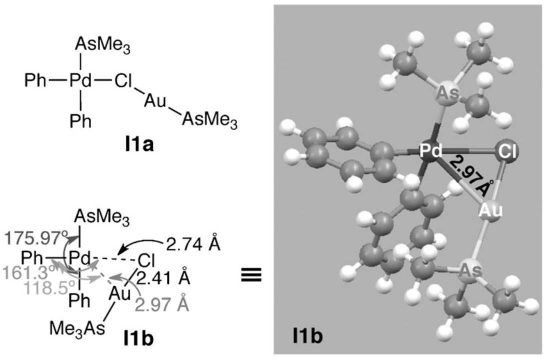


Figure 6. Calculated structure found for **I1**, induced by Au⋅⋅⋅Pd interactions, compared with a plausible structural alternative (**I1a**).

In conclusion, the study of the transmetalation in Au/Pd systems shows that aryl transmetalation from [AuArL] to [PdArXL$_2$] complexes is thermodynamically disfavored and will require a subsequent irreversible reductive elimination from [PdAr$_2$L$_2$] to form Ar−Ar and pull the reaction forward. The starting and final steps of the transmetalation process involve initial L release giving rise to a bimetallic system, and final L re-coordination splitting the metal–metal Pd−Au interaction. Strong Au−Pd interactions in the intermediates and transition states seem to be crucial to their stabilization. The Cl for R exchange step has the highest activation energy. The features observed herein might occur in other systems prone to produce metallophilic interactions (as observed in the Pt−Cu and Pt−Au cationic systems studied by Chen), and are particularly expected for heavier Group 10, 11, and 12 metals and their combinations.

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[8] This integrated expression corresponds to a second-order kinetics, $rate = k[\mathrm{A}][\mathrm{B}]$: J. H. Espenson, *Chemical Kinetics and Reaction Mechanisms*, *2nd ed.*, McGraw-Hill, Singapore, **1995**, pp. 19–22.

[9] This diphenyl complex cannot be handled experimentally for a transmetalation study because it immediately couples to give biphenyl.

[10] The ωB97X-D hybrid functional was used. Initially the BL3LPY functional was tried, but it failed to produce the experimentally required energy order $\mathbf{TS_1} < \mathbf{TS_2}$.

[11] The good energy fitting with the model might be due to two timely circumstances: 1) because of the bigger size of As relative to P, the cone angles of $AsMe_3$ and $AsPh_3$ are smaller than for the phosphanes, and steric effects become less important; 2) there must be a fortunate compensation of electronic effects making similar the experimental complex and the DFT model. Calculations on other complexes, including the experimental one, are being done to study these effects.

[12] **TS1** is a late transition state with the leaving arsane still keeping a very weak interaction with Pd at a very long distance of 3.14 Å.

[13] In the profile depicted in Figure 4 the labels **M1**–**M4** stand for the DFT models of the experimental compounds **1**–**4** and **I1** and **I2** stand for **A** and **B**, respectively.

[14] These differences are in the order of calculations on real molecules containing transition metals. For other examples comparing theoretical versus experimental values, see: M. García-Melchor, B. Fuentes, A. Lledós, J. A. Casares, G. Ujaque, P. Espinet, *J. Am. Chem. Soc.* **2011**, *133*, 13519–13526, and references therein.

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[18] Such a long Pd–Cl distance is better understood as a largely ionic bonding. We have found in the literature only one example, the cation $[Pd_2(\mu\text{-(dmb)}_4(\mu\text{-Cl})]^+$ (dmb = 1,8-diisocyano-*p*-menthane), which contains a Pd-Cl-Pd fragment with a Pd–Cl distance of 2.7143(6) Å, and a Pd-Cl-Pd angle of 180.0(1)°. The cation is described as a chloride anion encapsulated in a $[Pd_2\{\mu\text{-(dmb)}_4\}]^{2+}$ cation: T. Zhang, M. Drouin, P. D. Harvey, *Inorg. Chem.* **1999**, *38*, 1305–1315.