CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201301840

A Theoretical DFT-Based and Experimental Study of the Transmetalation Step in Au/Pd-Mediated Cross-Coupling Reactions

Max M. Hansmann,[a, b] Markus Pernpointner,*[b] René Döpp,[a] and A. Stephen K. Hashmi*[a, c]

Abstract: In this work a combined theoretical and experimental investigation of the cross-coupling reaction involving two metallic reaction centers, namely gold and palladium, is described. One metal center (Au) hereby is rather inert towards change in its oxidation state, whereas Pd undergoes oxidative insertion and reductive elimination steps. Detailed mechanistic and energetic studies of each individual step, with the focus on the key transmetalation step are presented and compared for different substrates and ligands on the catalytic Pd center. Different aryl halides (Cl, Br, I) and aryl triflates were investigated. Hereby the nature of the counteranion X turned out to be crucial. In the case of X = Cl and L = PMe_3 the oxidative addition is rate-determining, whereas in the case of X = I the transmetalation step becomes rate-determining in the Au/Pd-cross-coupling mechanism. A variety of Au–Pd transmetalation reaction scenarios are discussed in detail, favoring a transition state with short intermetallic Au–Pd contacts. Furthermore, without a halide counteranion the transmetalation from gold(I) to palladium(II) is highly endothermic, which confirms our experimental findings that the coupling does not occur with aryl triflates and similar weakly coordinating counteranions—a conclusion that is essential in designing new Au–Pd catalytic cycles. In combination with experimental work, this corrects a previous report in the literature claiming a successful coupling potentially catalytic in both metals with weakly coordinating counteranions.

Keywords: density functional calculations · gold · halides · palladium · transmetalation

Introduction

Cross-coupling reactions have become one of the key processes for C–C bond-formation in organic chemistry.[1] Whereas one transition metal, for example, palladium, readily undergoes oxidative addition and reductive elimination processes, the organic coupling partner is introduced by transmetalation from a redox stable main-group organometallic reagent most commonly derived from B, Sn, Li, Mg, Si, and so on (Figure 1). In the case of a transmetalation reagent that is based on a d-block metal, such as seen in the Sonogashira reaction (Cu), it is possible to classify these transformations as bimetallic catalytic systems.[2] These coupling reactions combine the advantages of two metal centers in a catalytic cycle, whereas at the same time they dramatically increase the complexity of the system; both metals having their own coordination sphere, ligand sets, and

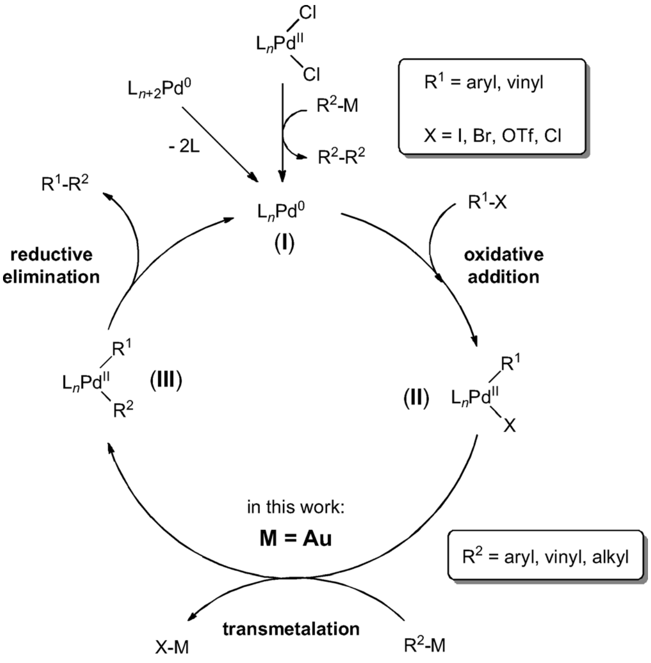


Figure 1. Key steps involved in the general palladium-catalyzed cross-coupling catalysis cycle.

---

[a] M. M. Hansmann, Dr. R. Döpp, Prof. Dr. A. S. K. Hashmi
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270
69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de

[b] M. M. Hansmann, Dr. M. Pernpointner
Institut für Physikalische Chemie, Theoretische Chemie
Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 229
69120 Heidelberg (Germany)
E-mail: Markus.Pernpointner@pci.uni-heidelberg.de

[c] Prof. Dr. A. S. K. Hashmi
Chemistry Department, Faculty of Science
King Abdulaziz University, Jeddah 21589 (Saudi Arabia)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301840.

redox-potentials. The various coupling mechanisms known in the literature are mainly discerned by the type of metals carrying the species to be coupled (Figure 1).

In the recent past the role of gold as a cross-coupling catalyst has been discussed, but seemingly homogenous gold catalysts are not able to efficiently undergo oxidative addition with R^1–X.[3] This creates an "orthogonality"[3b] in catalysis, which might lead to synthetically interesting selectivities, the assumed disadvantage might be fruitfully exploited by a combination of two metal-catalyzed cycles exhibiting orthogonal reactivity as shown in the seminal work by Hashmi et al.[4] and Blum et al.[5] Although the transmetalation of organogold-compounds to several redox-active transition metals such as Pd,[3b,4–6] Rh,[7] Ni,[8] Zr,[9] Ru, and Fe[10] has been studied by employing a stoichiometric amount of organogold species,[11] it is a challenging task to develop a double catalytic cycle in which the transmetalation reagent (R–Au–L) is generated in situ in a separate catalysis cycle (Figure 2).

As the gold-catalysis cycle in general is dependent on a highly cationic gold species (L–Au^+; usually generated by silver-abstraction of the corresponding L–Au–Cl compound)[12] and the transmetalation is driven by the formation of the Au–X bond, a seemingly conflictive scenario is generated. One solution to this "counteranion problem" is the use of terminal alkynes, the corresponding Au-acetylides can be generated from the L–Au–Cl complexes without activation by silver additives, leading to an Au-catalyzed Sonogashira-type reaction.[3a,13] Besides the use of terminal alkynes, the concept of dual-catalytic Pd/Au cycles is very scarce.[5a,14]

One major drawback recently pointed out by Gagné and Weber is the fact that Pd/Au redox-incompatibilities can be crucial.[6e] In our opinion, the lack of further reports on Pd/Au dual catalysis is additionally affected by the need for a counteranion that is weakly coordinating for the Au catalysis and, at the same time, is efficient enough in generating a driving force in the transmetalation step, an issue that is a major focus of this article. The counteranion problem was nicely solved for a very special system by Blum et al.[5a] utilizing a palladium-catalyzed cleavage of an allylic ester by formation of the palladium-π-allyl species circumventing the use of strongly coordinating halogen atoms, even if in this specific case it is questionable if palladium on its own can catalyze this transformation.[3b,15]

We were highly interested in understanding the mechanism and the thermodynamics of the gold–palladium transmetalation step from a theoretical and experimental point of view with a focus on the counteranion involved in this process to develop new dual-metal-catalyzed reactions. Very recently, Espinet et al.[16] analyzed the transmetalation step and prompted us to publish our results on this dual-catalytic system. The crucial effect of the counteranion in the transmetalation process has not been studied so far but seems in our opinion essential to understand and develop dual-catalyzed reactions.

As the transmetalation from the more noble (more electronegative) gold to the less noble (less electronegative) palladium seems thermodynamically counterintuitive, a detailed theoretical investigation supporting the experimental findings was of prominent interest. Here we report a computational study of the whole catalytic cycle from Figure 1 with two different ligand systems (monodentate and bidentate) on palladium, namely [Pd(dmpe)] (dmpe = 1,2-bis(dimethylphosphino)ethane) and $[Pd(PMe_3)_2]$ and the coupling fragments R^1 = phenyl and R^2 = vinyl in the form of Me_3PAu–vinyl. Whereas vinyl gold intermediates involved in the Au^I catalytic cycle are experimentally[17] and theoretically[18] well-studied, relatively little is known about their reac-

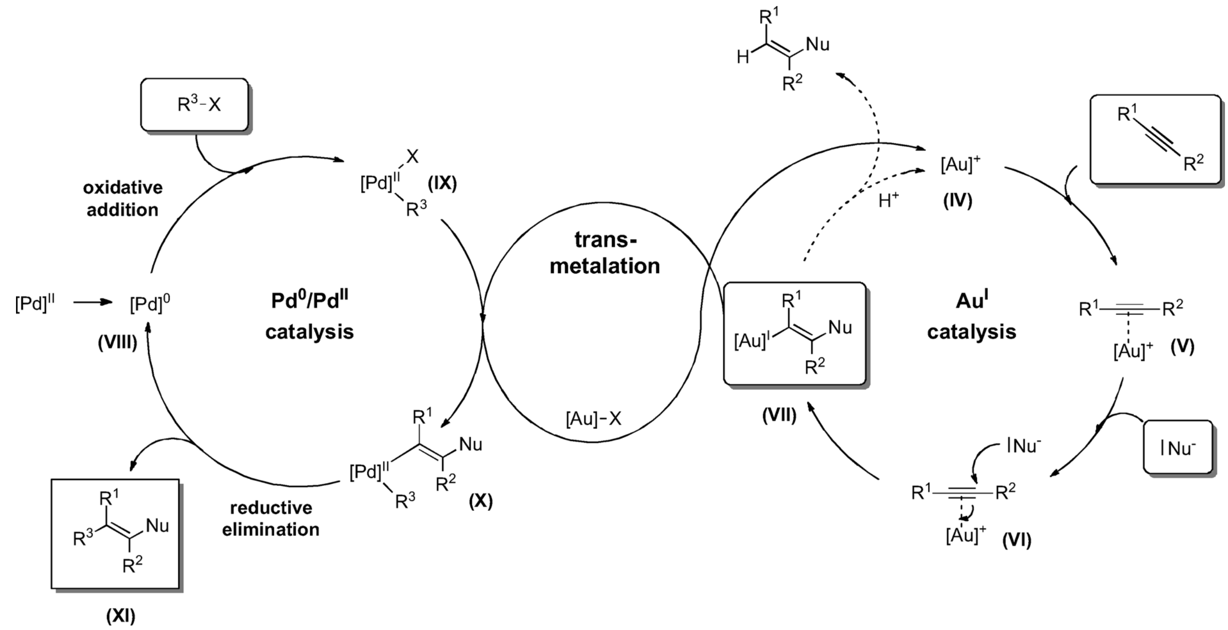


Figure 2. Dual-metal catalysis: combining palladium and gold catalysis.

tivity as transmetalation agents.[6] Two major aspects deserve special attention: First, it was experimentally observed that different halogen atoms X in the Ph−X species lead to very different yields in the overall reaction.[4,6c] All steps were therefore calculated for X = Cl (lowest reactivity) and X = I (highest reactivity) starting from the oxidative addition step. Secondly, a non-chelating (PMe_3) and a chelating (dmpe) ligand on the Pd substrate were considered to clarify the mechanistic details in the crucial transmetalation step (Figure 3).

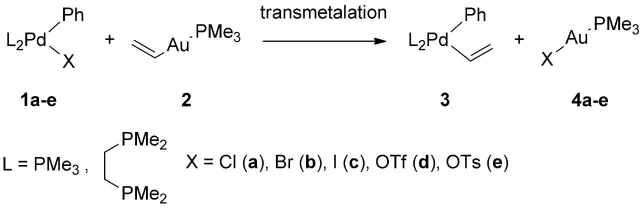


Figure 3. The key step: transmetalation from gold to palladium.

Computational Details

All calculations were performed by employing the Gaussian 03 program package.[19] The theoretical approach was the framework of density functional theory (DFT)[20] in combination with relativistic pseudo-potentials for both Au[21] and Pd[22] and the hybrid B3LYP functional.[23] The pseudo-potential basis sets and the all-electron basis sets for the light elements were of cc-pVDZ quality for the combined two-center systems and of cc-pVTZ quality for the smaller subunits. Due to the size of the transmetalation complex, augmented or triple zeta bases could not be employed in this case. All transition states were uniquely characterized by occurrence of one imaginary frequency and sought by the quadratic synchronous transit (QST3) algorithm.[24] As soon as the starting material, transition state, and product structures were available, the resulting reaction profile was verified by following the intrinsic reaction coordinate (IRC) as described in the literature.[25] Free reaction enthalpies were calculated for standard conditions (1 atm, 298 K) and are not corrected.

Computational Results

Global thermodynamic analysis of the cross-coupling reaction and the transmetalation step: As shown in Figure 4 and Table 1, initially for the overall cross-coupling reaction the differences in the electronic energy of the reactants and products were calculated at the DFT/B3LYP and MP2/RECP level of theory for X = Cl, Br, I, trifluoromethanesulfonate (OTf), and 4-toluenesulfonyl (OTs; **5a–e**) disregarding solvent effects for these neutral species.[26] For all ligands and methods the cross-coupling reaction between an organogold(I) species and an aryl halide or aryl triflate is thermodynamically clearly exothermic and exergonic (with only a small entropy contribution), whereas the reactivity within the halides increases from the chloride to the iodide. This is in accord with experimentally determined Ar−X bond dissociation energies, which amount to 96 (X = Cl), 81 (X = Br), and 65 kcal mol^{-1} (X = I).[27] The same trend is consistent with the bond-dissociation energies for the Au−X fragment obtained in high-level CCSD(T) calculations and FT-ICR-MS experiments corroborating the DFT trends.[28] The experiments show that aryl iodides lead to high yields in corresponding cross-coupling reactions, whereas only few conversions are known for aryl chlorides.[4,6c] A possible reason for the significant decrease of the overall thermodynamics for the TfO^- and TsO^- counteranions is the much weaker Au−OTf and Au−OTs bond (compared with the Au−I bond).

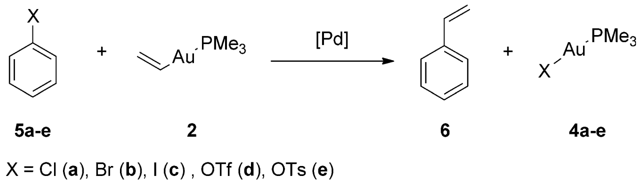


Figure 4. Global reaction for the palladium-catalyzed cross-coupling of organogold species.

Table 1. Total electronic energies of the global reaction (Figure 4) for different methods.

X	$E_{\text{DFT/B3LYP}}$ [kcal mol^{-1}]	$E_{\text{MP2/RECP}}$ [kcal mol^{-1}]
Cl (**a**)	−43.728	−38.906
Br (**b**)	−48.100	−43.933
I (**c**)	−52.723	−47.585
OTf (**d**)	−38.245	–
OTs (**e**)	−30.541	–

On average the MP2 values are higher by about 5 kcal mol^{-1} but the relative trend in the overall thermodynamics is comparable for both methods. The thermodynamics of the isolated transmetalation step (Figure 5) are shown in Table 2.

Hereby the substrate and product structures with varying counteranion X were energetically optimized at the DFT/

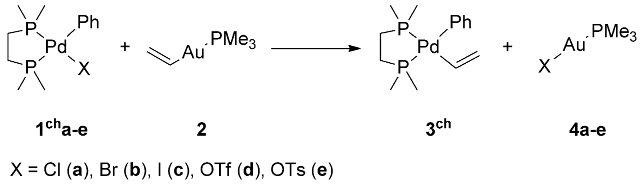


Figure 5. Thermodynamics of the transmetalation reaction.

Table 2. Thermodynamics of the transmetalation step (Figure 5) for various basis sets, methods, and tightness in the optimization.

X	E [kcal mol^{-1}][a]	E [kcal mol^{-1}][b]	E [kcal mol^{-1}][c]	E [kcal mol^{-1}][d]
Cl (**a**)	2.316	2.291	2.172	0.414
Br (**b**)	2.129	2.664	2.093	1.971
I (**c**)	1.857	1.856	1.738	4.246
OTf (**d**)	14.174	–	–	–
OTs (**e**)	13.991	–	–	–

[a] DFT/B3LYP, cc-pVDZ, normal convergence. [b] DFT/B3LYP, cc-pVDZ, tight convergence. [c] DFT/B3LYP, cc-pVTZ, normal convergence. [d] MP2/RECP, cc-pVDZ, normal convergence.

B3LYP and MP2/RECP level of theory together with the cc-pVDZ, cc-pVTZ, and LANL2DZ basis sets. The tightness of structure optimization was analyzed but proved to have only little influence.

The isolated transmetalation step is slightly endergonic at all levels of theory with comparable results for the individual halides (X = Cl, Br, I) at the DFT level (Table 2). Increasing the tightness of structure optimization, namely the threshold of the energy and norm of gradient vector, had only little influence on the thermodynamics but uses considerably more computational resources. The transition from a VDZ to a VTZ basis did not influence the DFT results significantly, justifying the use of the double zeta basis for all further calculations, which is important because a triple zeta basis cannot be employed for the large two-center complexes due to numerical bottlenecks.[29] The oxygen-bridged ligands are significantly raised in energy (X = OTf, OTs), which indicates a smaller tendency for the gold–oxygen bond formation as observed for the overall thermodynamics. No accurate experimental bond dissociation energies for the $PMe_3Au{-}X$ systems are available, which would be of great value to gain further insight into the transmetalation step.[28,30] To extend the systematic basis set test, we also tested the smaller LANL2DZ Pd basis set and an aug-cc-pVDZ Pd basis. Both variations led to very similar results in the transmetalation step, from which we deduced that an augmentation of the double zeta basis is not relevant and would lead to serious computational bottlenecks.

Analysis of the Au/Pd transmetalation mechanism employing monodentate phosphine ligands: We initially started our analysis of the transmetalation mechanism with the *trans*-$[PdXPh(PMe_3)_2]$ complex (*trans*-**1a**,**c**; X = Cl (**a**) or I (**c**)), formed after *cis–trans*-isomerization of the corresponding *cis* complex (*cis*-**1a**,**c**) after oxidative addition, and analyzed the two main transmetalation mechanisms:[31] Mechanism I) a dissociative or associative ligand substitution of the phosphine ligand with the vinyl gold compound leading to the intermediate **7a**,**c** followed via a 4-centered intramolecular transition state **8a**,**c** to the final transmetalation products, or mechanism II) a direct intermolecular vinyl-transfer from Au to Pd via a 4-centered transition-state **9a**,**c** followed by *cis–trans*-isomerization leading to the same transmetalation products (Figure 6). Both key transition states have in common a trigonal-pyramidal coordination sphere at the Au^I center, whereas the transition state **9a**,**c** would be pseudo-trigonal-pyramidal and **8a**,**c** square-planar in the coordination sphere of Pd^{II}.

Several attempts to locate a transition state **9a**,**c** according to mechanism II with various different methods and basis-sets failed. Based on our results, species **9a**,**c** is a transient species not exhibiting the required properties attributable to a transition state. Interestingly, we were able to locate a transition state according to **8a**,**c**, which connects the Au−C bond-breaking and Au−X bond-formation event in the coordination sphere of the palladium complex (Figure 7).

Remarkably, in these transition states the Au−Pd distance (2.722 for X = Cl and 2.804 Å for X = I) is much shorter than the van der Waals radii of gold and palladium combined. This indicates a significant metal–metal interaction lowering the activation energy for the R-group transfer. This is in good agreement with the very recent publications of Espinet et al. reporting on a structurally equal transition state with a nearly identical Pd−Au contact of 2.8 Å in the case of the corresponding chloro-arsan complex.[16] Furthermore, in this report we analyze the influence of the counteranion and give a complete theoretical analysis of the catalytic cycle, necessary to understand the rate-determining step in the total transformation.

The complete reaction path for the transmetalation through the *trans* complex is shown for both the chlorine and iodine counteranions in Figure 8. As expected, the *trans* complexes *trans*-**1a**,**c** are, by about 11 kcal mol^{-1}, more stable than the corresponding *cis* compounds (*cis*-**1a**,**c**), which are generated initially in the oxidative addition event and proved to be a sink on the energy potential surface.[32] Substitution of the PMe_3 ligand (associative or dissociative) followed by coordination leads to the Pd-η^2-vinyl complexes (**7a**,**c**), which requires approximately 12 kcal mol^{-1} in the absence of substantial entropic effects. Based on the work by Farina et al.[33a] and Amatore and Jutand et al.[33b] on the

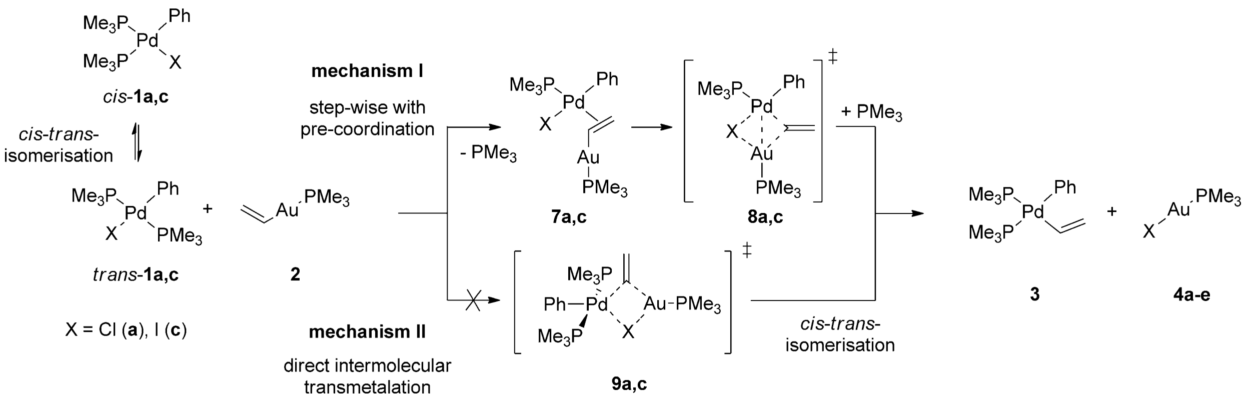


Figure 6. Model for a potential transmetalation mechanism with monodentate phosphine ligands.

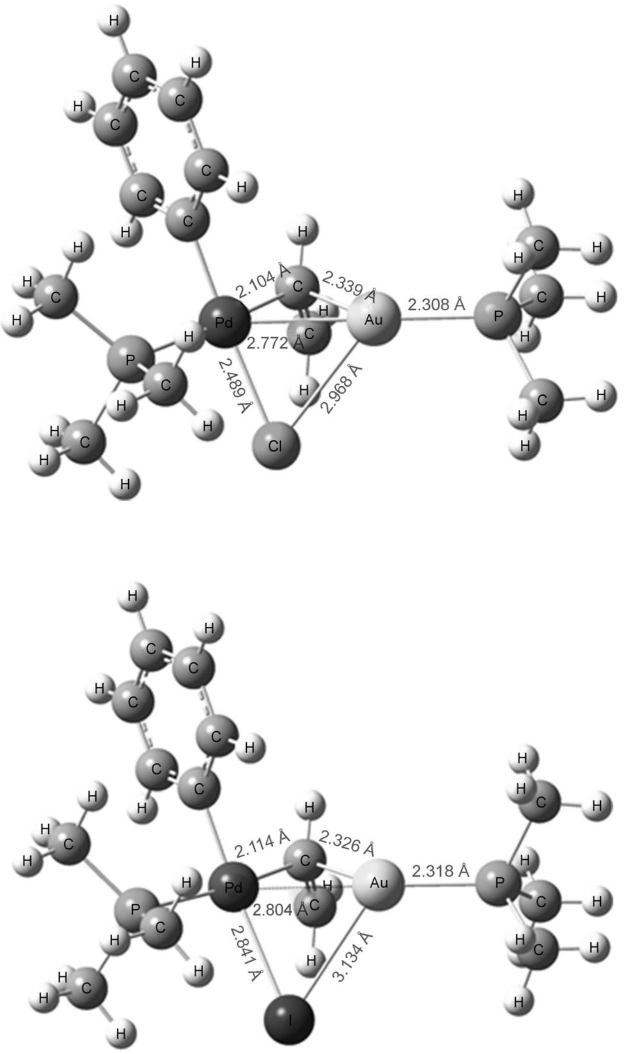


Figure 7. Transition state structures (**8a**,**c**) for the transmetalation step with X = Cl and X = I.

Stille reaction, in which a vinyl-transfer reagent is first bound in the coordination sphere of palladium prior to the transmetalation step as well, it seems very likely that the formation of the corresponding mixed Pd-vinyl-Au species **7a**,**c** is generated through a dissociative mechanism from *trans*-**1a**,**c**.

The theoretical results exhibit only a small difference on the activation energies for the transmetalation for the different counteranions ($\Delta G^{\neq}_{(\mathrm{I})} = 26.0\ \mathrm{kcal\,mol^{-1}}$; $\Delta G^{\neq}_{(\mathrm{Cl})} = 23.4\ \mathrm{kcal\,mol^{-1}}$) and in the energies of the product complexes **10a**,**c**, which is seemingly in contrast to the experimental findings that only for strongly activating ligands will chlorine compounds undergo the cross-coupling reaction.[4,6c] This can be explained by a change in the rate-determining step from transmetalation to oxidative addition depending on the counteranion, which will be approved in the section below and in the Experimental Section.

To generate the *cis*-[PdR_2L_2] precursor **3** from the transmetalation products still bound in the coordination sphere (**10a**,**c**) different scenarios are imaginable: The direct dissociation of **10a**,**c** into the X−Au−PMe_3 molecule (**4a**,**c**) and the T-shaped structure (compound **11**) seems electronically non-favored, but reasonable based on the large entropy contribution. Alternatively, an associative pathway with a solvent molecule (e.g., MeCN) or a phosphane ligand also seems reasonable to generate the final transmetalation complex **3** (Figure 8). It is noteworthy to highlight that the Au−Pd contacts, not only in the transmetalation transition states (**8a**,**c**), but also in the intermediates before and after the transmetalation step (**7a**,**c** and **10a**,**c**) are very short (see the Supporting Information) clearly demonstrating the importance of metal–metal interactions.

The overall thermodynamic data for the transmetalation step compared to the *cis*-complex [$PdXPhL_2$] (*cis*-**1a**,**c**) is $\Delta G_{trans} = +1.4\ \mathrm{kcal\,mol^{-1}}$ (X = Cl) and $\Delta G_{trans} = -0.9\ \mathrm{kcal\,mol^{-1}}$ (X = I), respectively, is in accord with the thermodynamic results for the transmetalation reaction employing the chelate ligand on Pd (Table 2). Interestingly, the transmetalation thermodynamics are highly endergonic $\Delta G_{\mathrm{trans}} = +13.5\ \mathrm{kcal\,mol^{-1}}$ (X = Cl); $\Delta G_{\mathrm{trans}} = +10.2\ \mathrm{kcal\,mol^{-1}}$ (X = I) if compared with the *trans*-[$PdXPhL_2$] complex (*trans*-**1a**,**c**), which is in good agreement with the experimental and theoretical results by Espinet et al.[16a] studying the favored (exergonic) transmetalation from Pd to Au starting with [PdR_2L_2]. The here studied corresponding reverse and thermodynamically upwards process can only be realized by coupling this process to a reductive elimination event pushing the equilibrium towards the desired cross-coupling products (see section below).

Analysis of the Au/Pd transmetalation mechanism employing a chelate ligand: In the second section of this discussion (see above) we could demonstrate a reasonable transmetalation mechanism based on the exchange of a monodentate phosphine ligand with the vinyl gold fragment followed by an intramolecular R-group transfer via a transition state showing close Pd−Au contacts. It is interesting to point out that this mechanism is closely related to the proposed mechanism of the deeply studied Stille coupling.[33] Interestingly, these transmetalation studies always employed monodentate ligands on the palladium center, easily opening a free coordination site by dissociation of a ligand on palladium. Our experiments, however, demonstrated that chelating ligands such as 1,1′-bis(diphenylphosphino)ferrocene (dppf) were very efficient ligands for the Pd-catalyzed cross-coupling of organogold species,[4,6c] raising the question how this transmetalation process can proceed if the ligand seemingly blocks the free coordination-site on the metal center that is essential for organogold pre-coordination prior to transmetalation. In Figure 9 our initial ideas are summarized on how a bidentate ligand can influence the change in the reaction pathway for the transmetalation step.

Pathway I is in analogy to Figure 6, a concerted mechanism passing through a four-membered transition state with local trigonal-bipyramidal coordination at palladium (**9**$^{\mathbf{ch}}$**a**–**e**). Analogous to the case of the monodentate phosphine

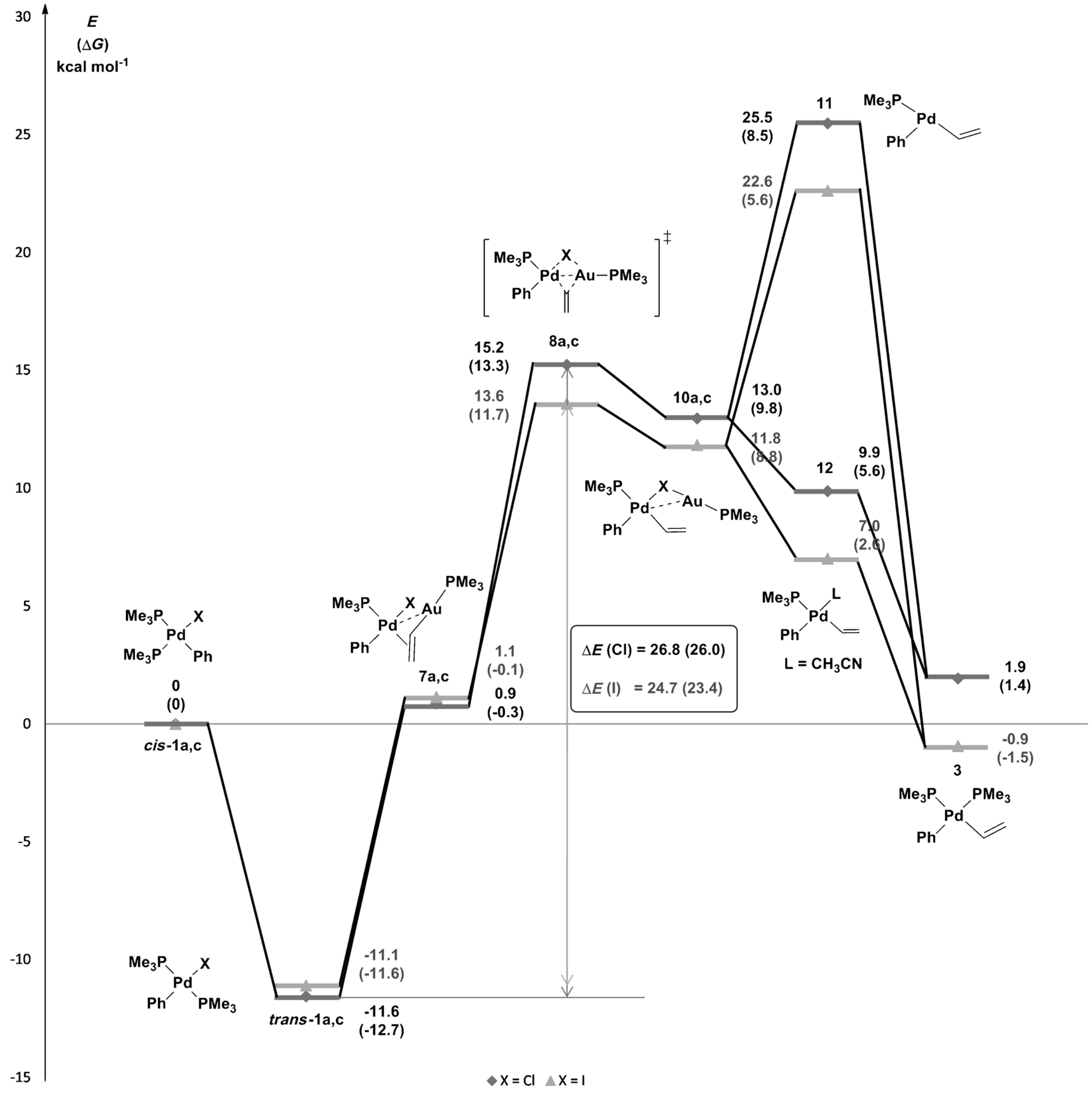


Figure 8. Reaction profile for the transmetalation pathway with monodentate ligands.

ligand system we were unable, even with very high efforts, to locate such a transition state, which is in accord with the search for a similar transition state in the Stille cross-coupling.[33c] From a computational point of view it may be possible that an even larger basis together with a more sophisticated method such as coupled cluster theory would lead to a localizable state, but as far as our tests revealed, such a transition state does not seem to be accessible. As a consequence, we suggest a multistep mechanism according to the dissociative pathways II or III: In II the Pd/X bond is heterolytically broken (**13^{ch}**) and the vacant coordination site occupied by the vinyl carrier (**14^{ch}**), whereas in III a chelate ring opening is discussed.

To classify the feasibility of transmetalation pathway II we calculated the bond-dissociation energy for the Pd–X bond (**13^{ch}**) in Figure 9 and obtained 128.98 (X = Cl), 123.66 (X = Br), and 113.79 kcal mol^{-1} (X = I), which indicates an energy barrier that is far too high for this pathway to occur in the gas phase under standard conditions. Certainly, solvents can considerably decrease this barrier by interaction with the resulting ions. For acetonitrile we simulated this solvation effect by adding one molecule of acetonitrile to the complex **13^{ch}** and obtained a noticeable energetic stabilization of 29.2 kcal mol^{-1}.

In contrast to the theoretical prediction, a considerable influence of the solvent could not be observed experimentally,[4] and therefore does not support an ionic dissociative

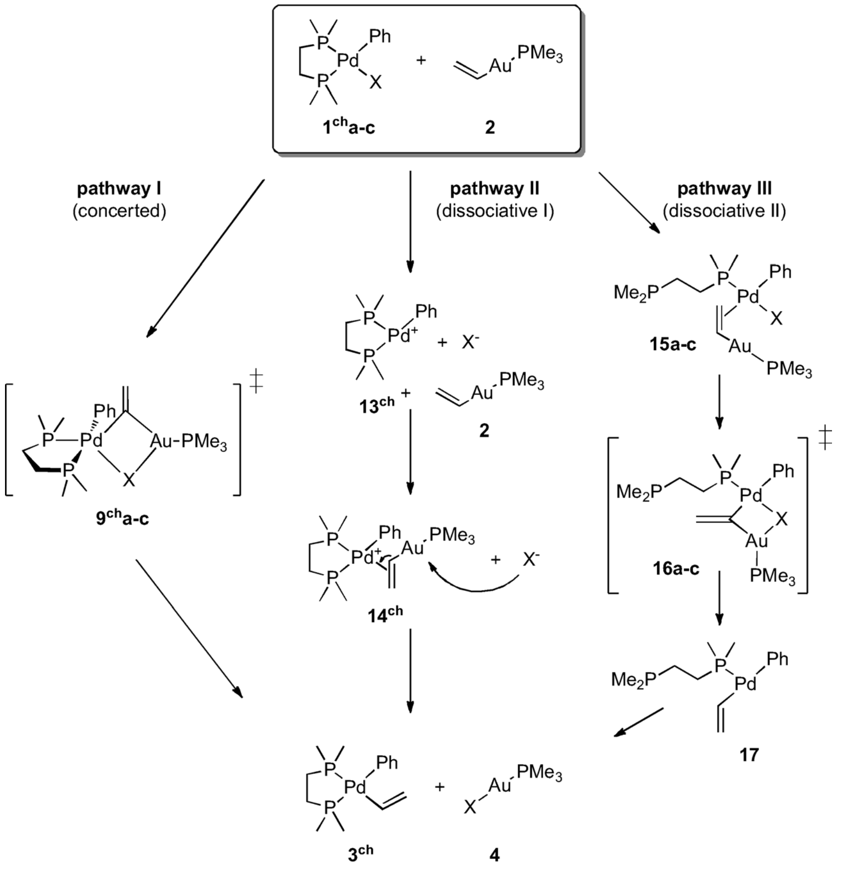


Figure 9. Proposed mechanisms for the transmetalation step utilizing a chelating ligand.

mechanism. Mechanisms of this type are only feasible if the counteranions are very weakly bound to the metal center, which is the case for, for example, triflate anions, but not for halides (e.g., see the discussion of the cationic Heck reaction[34]). For the current system, a triflate ligand (X=OTf) does not undergo any transmetalation reaction with Au and Pd as metal centers (see the section below). As a consequence, a purely dissociative mechanism including a cleavage of the Pd−X bond is very unlikely. A variation of this pathway emerges if one postulates an associative replacement of the X^- anion by the incoming vinyl ligand. The energy required for this variant can be obtained from the components **14**^{ch} and **2** (Figure 9) and amounts to 97.54 (X=Cl), 92.21 (X=Br), and 82.34 kcal mol^{-1} (X=I), which still represents a very unfavorable process. From these findings we deduce that a purely dissociative way under cleavage of the Pd−X bond is energetically too costly and may be intrinsically coupled to the formation of the Au−X bond.

As we successfully found a transmetalation pathway for monodentate ligands and we ruled out the Pd−X bond breakage, we envisioned the unusual possibility of a chelate opening to coordinate the organogold species according to the monodentate mechanism (Figure 9, pathway III).

The creation of a free coordination site on Pd is proposed due to the fact that a square-planar configuration is very much preferred by Pd^{II} over any higher coordination number. A fivefold coordination with the substrate occupying the apex of a quadratic pyramid immediately led to a reverse process forming the educts as we showed computationally. The employment of a larger basis set did not change these findings, having their origin in a high-lying p_z LUMO on Pd making the metal center unfit for a fast attack by the substrate. In Figure 10 the complete reaction path for the transmetalation under a chelate ring opening is presented for all three halides (X=Cl, Br, and I).

In a first step, the vinyl gold species (**2**) adds to the vacant coordination site on Pd being available after the opening of the chelate ring (**15**^{ch}**a–c**). The required energy for this step amounts to 7–9 kcal mol^{-1} (electronic) and 19–21 kcal mol^{-1} (free enthalpy; because this process is entropically disadvantageous), being quite independent of the X substituent employed. These energy differences lie within an accessible range for a thermal reaction and would allow for a ring opening. In the resulting intermediates **15**^{ch}**a–c** (Figure 10), the Au−Pd distance amounts to about 3.32 Å and is an indication for a possible interaction between the Au and Pd metal centers as seen with the monodentate phosphine ligands as well. Via a cyclic transition state, analogous to the ones in Figure 7, a concerted Au−C bond-breaking and an Au−X bond-forming takes place, followed by liberation of the X−Au−PMe_3 species from the complexes **15**^{ch}**a–c**, yielding the T-shaped intermediate **17**. This amount of energy required (≈30 kcal mol^{-1}) is nearly the same for all halides and renders this step quite unfavorable, but still in an acceptable range, as T-shaped structures of Pd complexes are known characterized intermediates.[35] An alternative to the T-shaped intermediate formation **17** is a coordination of the halide to the two metal centers as shown in structure **10**^{ch}**c**, which could be computationally characterized as an intermediate. By a possible assistance of the solvent molecules or phosphine ligand, the X−Au−PMe_3 species is expelled from the complex **10**^{ch}**c** and the final product **3** is formed by the favorite ring closure of the chelate ligand, enabling a lower-energy pathway. It should be pointed out that the chelate ring opening leads to a dramatic increase of conformational isomers making the computational localization of transition states a demanding task. As we could already demonstrate a successful transme-

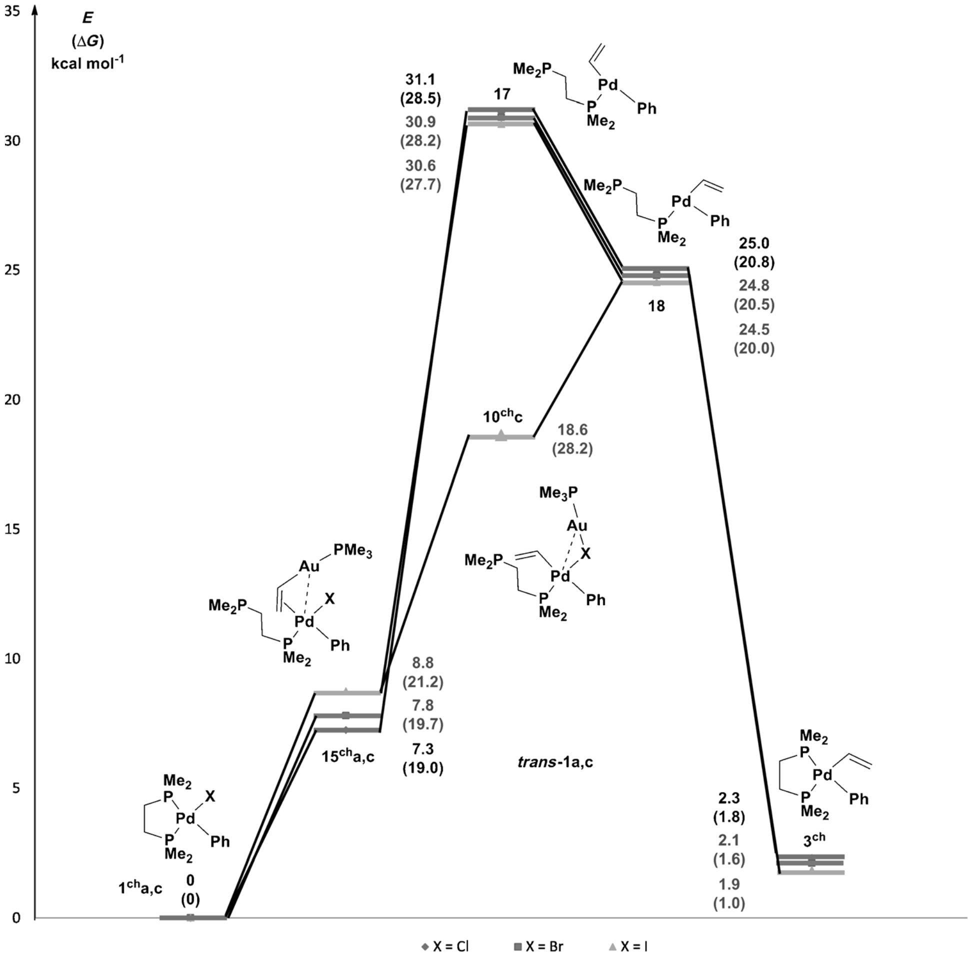


Figure 10. Calculated reaction profile for a transmetalation mechanism in the coordination sphere of Pd through a chelate opening.

talation pathway based on the easier to analyze monodentate phosphine model, and here could demonstrate that a chelate opening is energetically feasible (but entropically disadvantageous), we see no need for a further detailed analysis.

Further models for other potential transmetalation mechanisms: Beside our transmetalation models outlined above, we briefly mention some viable alternatives that were tested by us numerically. At first we investigated a nucleophilic attack of an iodine ion to the gold vinyl species producing an "aurate" compound that might transfer the organic group more easily because of the higher electron density. This is in analogy to the initial assumption of an "ate"-complex in the Suzuki reaction[36a] (even though it was later shown that not the "ate"-complex but a Pd-hydroxide species was the relevant transmetalation intermediate).[36b] A corresponding local minimum for an anionic trigonal-coordinated gold species could, however, not be detected computationally attributing only little probability to this variation. The same holds for an assumed radical mechanism due to the experimental finding that the addition of a radical-capturing reagent did not influence the transmetalation yields in any way.[4,6c] Despite the fact that Au does not exhibit a strong tendency to change its oxidation state during a reaction, a quadratic planar complex with an energetic minimum could be localized (Figure 11). This quadratic coordination is typical for Au^{III} complexes indicating a higher oxidation state, even if the oxidation states are difficult to assign in such bimetallic compounds. However, the Au–P and Au–Cl bond lengths are quite elongated (2.601 and 2.455 Å) and allow for the interpretation of an oxidative insertion of the vinyl gold species into the Pd–Cl bond. A corresponding transition state incorporating structure **19** was not found in the calculated pathway and the relevance of structure **19** with a significant Au/Pd interaction could therefore not be perfectly established.

Finally, a one-step process (Figure 12) through a [3+2] σ-bond metathesis was sought, skipping the explicit transmetalation step. Despite the fact that a reaction pathway starting from a distorted initial geometry derived from Figure 12 led to the desired products, an appropriate transition state could not be found and is necessary for a sound argumentation. This is in accordance with the experimental result that adding free phosphane ligands in-

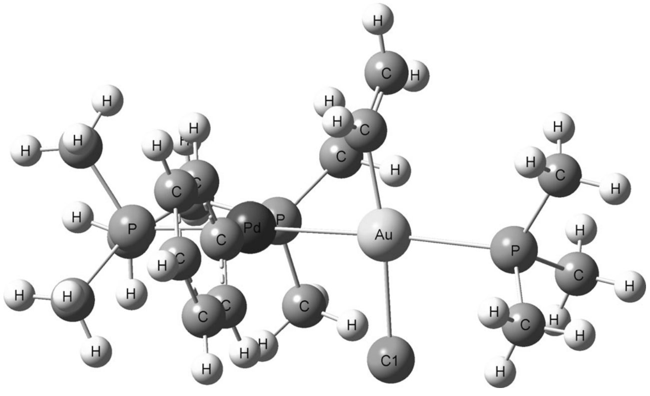


Figure 11. Structure of **19**: A local-minimum on the potential energy surface.

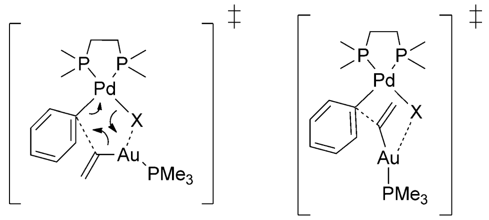


Figure 12. A potential one-step concerted R-group transfer.

hibits the reaction, which should not occur in a fully concerted mechanism and further supports our transmetalation mechanism outlined above in which phosphine pre-dissociation is necessary.

Global energy profile for the cross-coupling process: A simplified complete picture: After analyzing in detail the transmetalation step for two different ligand systems, we analyzed the full catalytic cross-coupling cycle, including oxidative addition and reductive elimination to gain insight into the rate-determining step of the complete catalysis cycle depending on the electrophile and the ligand system employed (Figures 13 and 14).

In the case of monodentate phosphine ligands (Figure 13; L = PMe_3) we observe a change of the rate-determining step depending on the counteranion employed. Whereas in case of X = Cl, the oxidative addition is non-favored with a high activation barrier ($\Delta G^{\neq}_{(Cl)} = 32.3\ \mathrm{kcal\,mol^{-1}}$) the corresponding oxidative addition into the C–I bond proceeds, as expected, with a lower activation energy ($\Delta G^{\neq}_{(I)} = 22.5\ \mathrm{kcal\,mol^{-1}}$). As the activation energy for the transmetalation process only differs slightly between the different halogen counteranions, the rate-determining step changes from the oxidative addition (X = Cl) to the transmetalation (X = I; $\Delta G^{\neq}_{(I)} = 23.3\ \mathrm{kcal\,mol^{-1}}$), respectively.

We analogously calculated the process for the chelate [Pd(dmpe)] system and summarize here the main differences. As the bent 14 valence electron (VE) Pd^0 species is more activated towards oxidative addition compared with the linear Pd^0 species, the oxidative addition proceeds even in the case of X = Cl, with a much lower activation energy ($\Delta G^{\neq}_{(Cl)} = 14.5\ \mathrm{kcal\,mol^{-1}}$).[37] With the bidentate ligand system employed, both transmetalation events (X = Cl, I) proceed through relatively high-energy pathways through opening of the chelate ring and represent the rate-determining step (Figure 14).

In summary, the transmetalation step from Au to Pd is in both ligand cases an endergonic process, which is driven by the highly exergonic reductive elimination event. Whereas the ligand system on palladium most effectively changes the

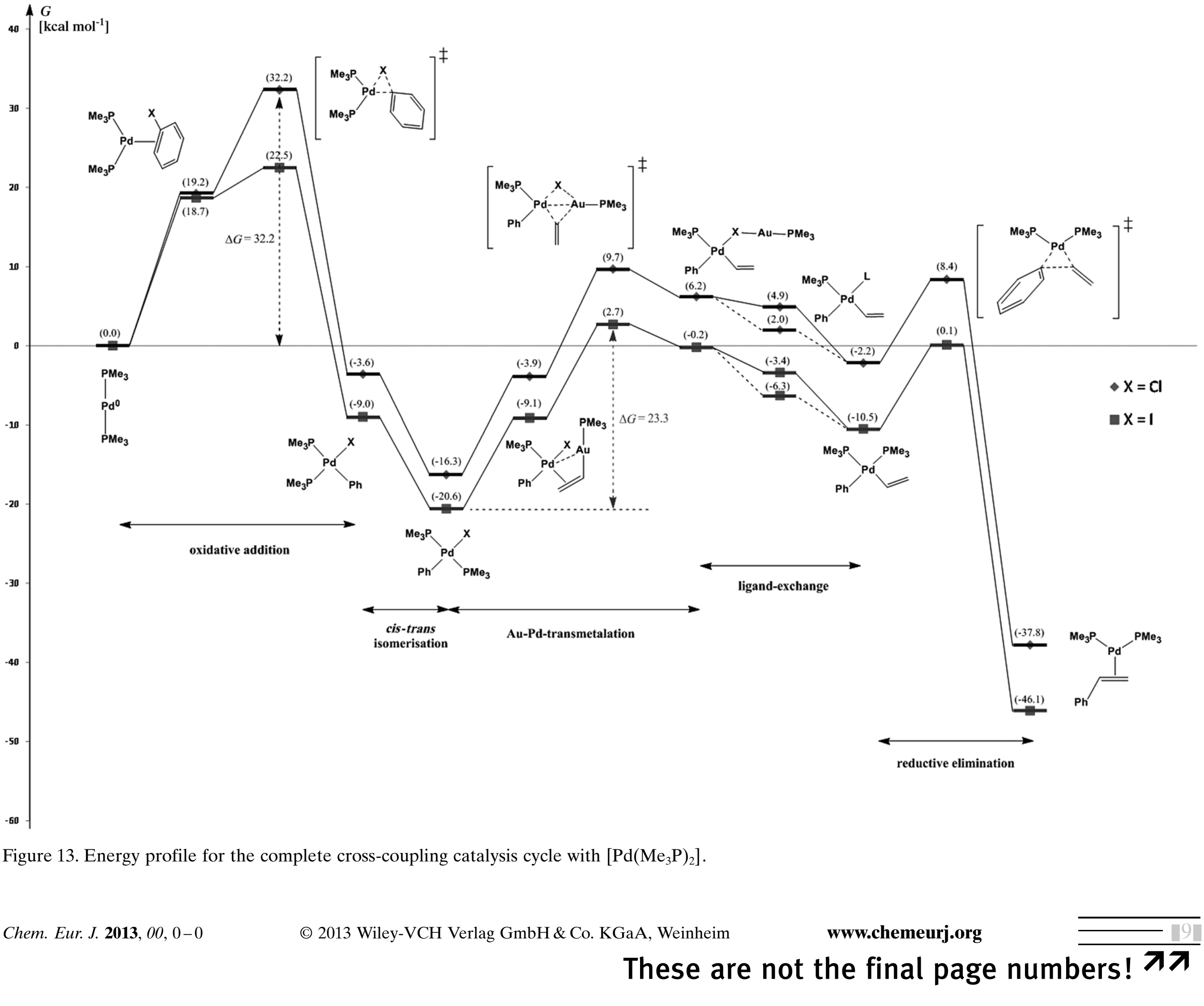


Figure 13. Energy profile for the complete cross-coupling catalysis cycle with $[Pd(Me_3P)_2]$.

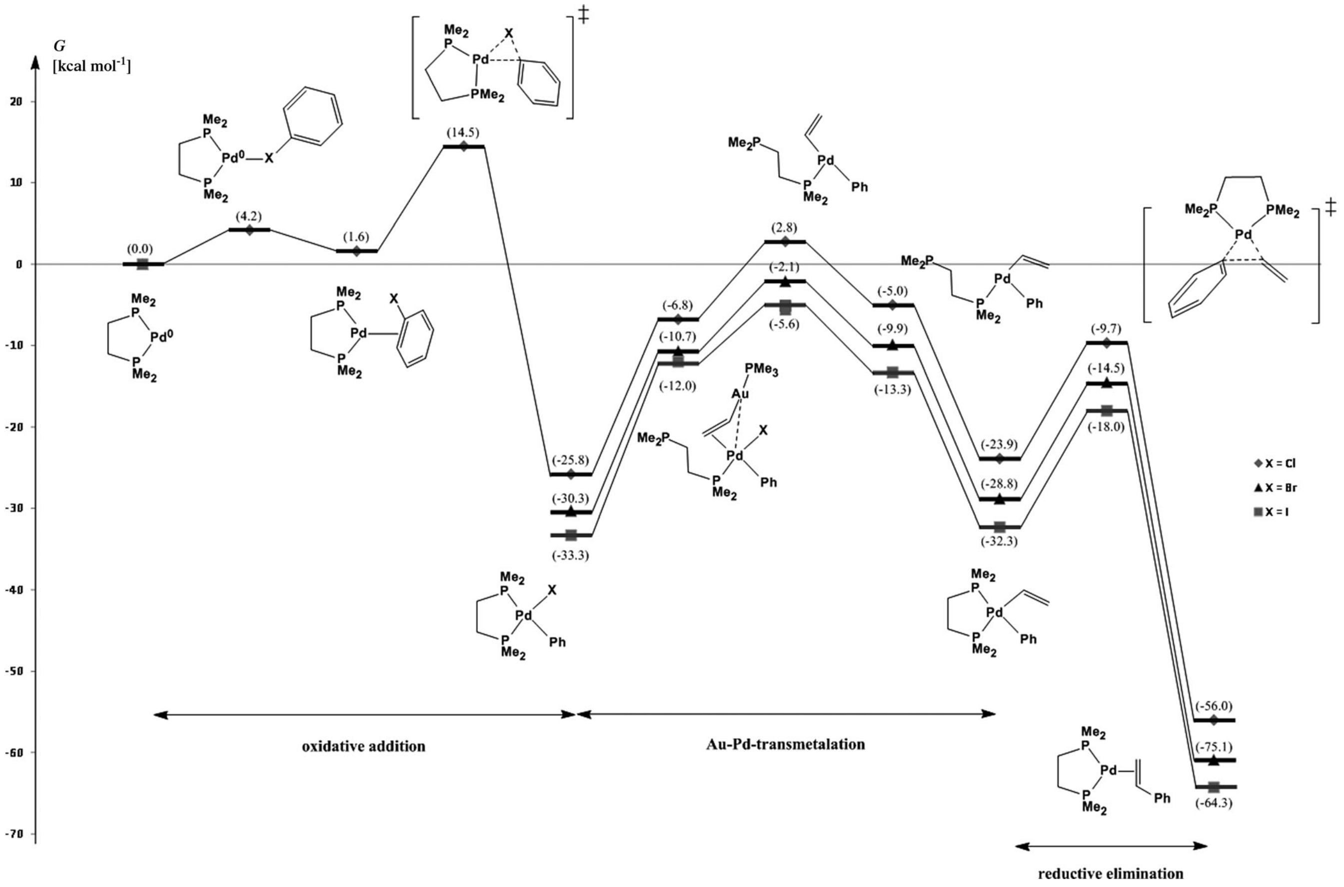


Figure 14. Energy profile for the full cross-coupling catalysis cycle with [Pd(dmpe)].

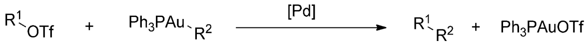
activation barrier of the oxidative addition, it almost has no effect on the reductive elimination.

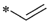
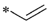
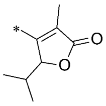
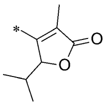
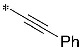
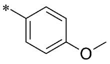
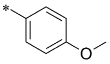
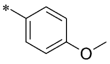
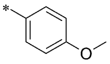
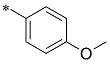
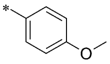
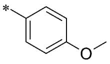
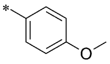
Experimental Results

The role of the counteranion: Based on our protocol for the palladium-catalyzed cross-coupling reactions of aryl-, heteroaryl-, vinyl-, alkynyl-, benzyl-, or acyl halides with stoichiometric amounts of an organogold compound, we wanted to experimentally verify the computational results on the counteranions in our outlined transmetalation mechanism and reinvest the role of triflates as electrophiles. A series of experiments with phenyltriflate and 4-acetylphenyltriflate were performed (Table 3). Unfortunately, all attempts to use aryl triflates in our cross-coupling protocol failed (Table 3, entries 1–6).

Even with the Pd/XPhos system (XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), which is a very active catalyst in Suzuki–Miyaura coupling of aryl triflates, no cross-coupling product was detected (Table 3, entry 2). Methyl triflate (Table 3, entry 6) and phenyl triflimide also gave no cross-coupling products. To our surprise, a palladium-catalyzed cross-coupling reaction with aryl triflates was published a few months after our own unsuccessful attempts.[6d] Aryl triflates were coupled with various organogold compounds and the products were obtained in moderate to high yields.[6d,38] The reaction conditions published were very similar to our conditions with one major difference: the organogold compounds had not been isolated in a preceding synthetic step but prepared in situ from organolithium compounds and [AuCl(Ph_3P)]. Thus, one equivalent of LiCl is present in the cross-coupling reactions from ref. [6d]. Based on these insights, we repeated our experiments adding stoichiometric amounts of various salts. Small amounts of cross-coupling products were formed in the absence of any halide (Table 3, entries 7 and 8). In contrast, the presence of halides in the reaction mixture immediately increased the yields to 77–99 % (Table 3, entries 9–12). The type of halide source did not have a strong influence on the yields. This fully confirms our computational results for the transmetalation step, demonstrating 1) no significant difference between the halide counterions in the transmetalation step and 2) a significant difference between the halides and the oxygen-based counteranions. As shown in Table 2, the thermodynamics of the transmetalation reaction are only slightly endergonic in the case of X = Cl, Br, I ($\approx$1-4 kcal mol^{-1}) but strongly endergonic for X = OTf ($\approx$14 kcal mol^{-1}). The oxidative addition of the Pd^0 species into ArOTf leads to a cationic [PdAr(S)L_2]$^+$ complex, which can only form the Au–OTf bond in the transmetalation event; an energetically non-favored process outlined in Table 2. In the presence of a halide source a Pd–X triflate–halide exchange leads to the neutral [PdCl(Ar)L_2] complex,[39] which

Table 3. Palladium-catalyzed cross-coupling of organogold compounds with aryl triflates.

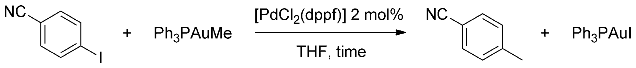


Entry	R^1 ([equiv])	R^2 ([equiv])		Catalyst ([mol %])	Additive	Solvent	T [°C]	t [h]	Yield [%]
1	Ph (1.5)		(1.0)	[$PdCl_2$(dppf)] (10.0)	–	MeCN	RT	24	0
2	Ph (1.5)		(1.0)	Pd/XPhos (5.0)	–	MeCN	RT	4	0
3	4-AcPh (1.5)		(1.0)	[$PdCl_2$(dppf)] (1.0)	–	MeCN	60	11	0
4	4-AcPh (1.5)		(1.0)	[$PdCl_2(PPh_3)_2$] (2.0)	–	THF	60	10	0
5	4-AcPh (1.5)		(1.0)	[$PdCl_2(PPh_3)_2$] (2.0)	–	THF	RT	4	0
6	Me		(1.1)	[$PdCl_2$(dppf)] (2.0)	–	MeCN	RT	16	0
7	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	–	THF	RT	18	6
8	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	LiOTf	THF	RT	18	9
9	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	LiCl	THF	RT	18	95
10	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	LiBr	THF	RT	18	90
11	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	Bu_4NCl	THF	RT	18	99
12	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	Bu_4NBr	THF	RT	18	97
13	4-AcPh (1.0)		(1.1)	[$PdCl_2(PPh_3)_2$] (5.0)	Bu_4NI	THF	RT	18	77

allows a transmetalation mechanism involving a halide bridged Pd–X–Au transition state (Figure 7) that fully explains these experimental findings. At this stage it cannot be ruled out that for the oxidative addition a halide effect results in an acceleration through the formation of anionic palladate complexes.[40] But the complete experimental failure of transmetalation with the triflates can only be explained by the transmetalation not taking place, as the oxidative addition of aryl triflates especially in the presence of Pd/XPhos is known to be possible even without halides. It is interesting to note that in the case of the Stille reaction, the addition of LiCl improves the rate for the oxidative addition but has a retarding effect on the transmetalation step,[33g,39] an effect that is in stark contrast to the corresponding organogold transmetalation in which the driving force is generated through the formation of the Au–X bond. Furthermore, it is in accord with our calculations that palladium-catalyzed cross-coupling reactions of organogold-species with aryl bromides and aryl chlorides are mainly effected by the ligand system on palladium to undergo the oxidative addition process (Figures 13 and 14), whereas the transmetalation proceeds equally well with different halides but not triflates. In situ-exchange of triflate with a halogen counterion re-establishes the transmetalation step, but raises problems in the double catalytic Pd/Au catalysis, as a non-activated non-cationic Au–X species would not undergo classical gold-catalyzed transformations.

In ref. [6d] alkyl gold species were also used in cross-coupling reactions. Under our typical conditions, [Au(CH_3)Ph_3P] was not effective in the cross-coupling reaction. This may be due to its insolubility in MeCN. However, in THF the cross-coupling was successful. At room temperature after 18 h only 27 % yield of the product was obtained (Table 4, entry 1). A longer reaction time of three days gave only a minor improvement to 29 % (entry 2). Increasing the temperature to 60 °C gave 65 % after 18 h (Table 4, entry 3) and 83 % yield after three days (entry 4). Overall, compared with other organogold compounds (vinyl-, aryl-, and also

Table 4. Cross-coupling experiments with alkyl gold species.



Entry	T [°C]	t	Yield [%]
1	RT	18 h	27
2	RT	3 d	29
3	60	18 h	65
4	60	3 d	83

Hammond-type vinyl gold species), the alkyl species seemed to be less reactive. These experiments are also consistent with the calculated mechanism. Chen et al. could isolate the structurally similar Pt^{II}–Cu^{I} and Pt^{II}–Au^{I} complexes with a methyl group coordinated in the coordination sphere of Pt^{II}.[41] This indicates that a mechanism based on pre-coordination even in the case of alkyl gold species is reasonable, but less favored, which is nicely in accord to our theoretical findings.

Conclusion

In this work a new palladium-catalyzed C–C-coupling reaction with an organogold-compound as the transmetalation reagent was theoretically investigated at the DFT/B3LYP and partially at the MP2 level of theory. Several potential transmetalation scenarios were analyzed with a monodentate- and bidentate-ligand system and were fit into the context of the full cross-coupling energy profile. We could locate a transmetalation mechanism based on pre-coordination of the organogold-species followed by transmetalation in the coordination sphere of palladium via a transition state exhibiting very short intermetallic Au–Pd contacts. This transmetalation mechanism is in very good agreement with the theoretical studies reported on the Stille reaction[33] and very recent reports by Espinet et al.[16] Furthermore, by analyzing the full energy profile we could locate a change in the rate-determining step depending on the counteranion and the ligand system involved; in the case of X = Cl the oxidative addition is the rate-determining step, whereas in the case of X = I it is the transmetalation (with $L = PMe_3$). Employing a chelating ligand system on palladium significantly lowers the activation barrier for the oxidative-insertion process and determines the transmetalation to be rate-determining. Whereas the thermodynamics of the Au–Pd transmetalation step are endergonic, the switch from a halogen (X = Cl, Br, I) to an oxygen-based counteranion (OTf) proved to dramatically increase the activation barrier for a successful transmetalation event. In combination with the performed experiments we could demonstrate that the cross-coupling reaction is only accessible with aryl triflates in the presence of additional halides sources (such as LiCl). This clearly supports our theoretical work suggesting a triflate–halogen exchange after oxidative addition followed by our outlined mechanism. This is important information for the further development of new Pd/Au dual-catalyzed reactions because it highlights the problem of the use of weakly coordinating counteranions together with the cross-coupling strategy.

Experimental Section

General methods: All reagents and solvents were obtained from Fisher Scientific, ABCR, Alfa Aesar, Sigma–Aldrich, or VWR and were used without further purification unless otherwise noted. Absolute solvents were dried by a MB SPS-800 using drying columns. Preparation of air- and moisture-sensitive materials was carried out in flame dried flasks under an atmosphere of nitrogen using Schlenk techniques. Thin layer chromatography (TLC) was performed using Polygram pre-coated plastic sheets SIL G/UV_{254} (SiO_2, 0.20 mm thickness) from Macherey–Nagel. Yields have been determined by GC using *n*-dodecane as internal standard for quantification.

General procedure for the cross-coupling of organogold-compounds with aryl triflates: Under a nitrogen atmosphere, the organogold compound (1.0 equiv), aryl triflate (1.5 equiv), palladium catalyst, and (in some cases) an additive (1.2 equiv) were dissolved in dry solvents and stirred for the specified time. *n*-Dodecane (1.0 equiv) was added and the reaction mixtures were analyzed by GC or GC-MS (Quantification by GC).

General procedure for the cross-coupling with methyl(triphenylphosphine)gold(I): $[Au(CH_3)Ph_3P]$ (47.4 mg, 110 μmol), 4-iodobenzonitrile (22.9 mg, 100 μmol) and $[PdCl_2(dppf)]$ (1.46 mg, 2.00 μmol) were dissolved in dry THF under nitrogen atmosphere. *n*-Dodecane (23.0 μL, 100 μmol) was added and the reaction mixture was stirred for three days and analyzed by GC-MS.

Acknowledgements

The authors thank Umicore AG & Co. KG for the generous donation of gold salts. M.M.H. is grateful to the Fonds der Chemischen Industrie for a Chemiefonds scholarship and the Studienstiftung des deutschen Volkes.

---

[1] *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.

[2] a) M. H. Pérez-Temprano, J. A. Casares, P. Espinet, *Chem. Eur. J.* **2012**, *18*, 1864–1884; b) O. F. Wendt, *Curr. Org. Chem.* **2007**, *11*, 1417–1433.

[3] a) T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet, A. M. Echavarren, *Org. Lett.* **2010**, *12*, 3006–3009; b) A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Ackermann, J. D. B. Becker, M. Rudolph, Christian Scholz, F. Rominger, *Adv. Synth. Catal.* **2012**, *354*, 133–147; in the presence of a strong oxidant or a fluoride source, Au^{I} is capable of undergoing oxidative cross-coupling reactions without the involvement of a second metal; for selected examples, see: c) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *J. Organomet. Chem.* **2009**, *694*, 592–597; d) G. Zhang, Y. Peng, L. Cui, L. Zhang, *Angew. Chem.* **2009**, *121*, 3158–3161; *Angew. Chem. Int. Ed.* **2009**, *48*, 3112–3115; e) G. Zhang, L. Cui, Y. Wang, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474–1475; f) A. S. K. Hashmi, T. D. Ramamurthi, M. H. Todd, A. S.-K. Tsang, K. Graf, *Aust. J. Chem.* **2010**, *63*, 1619–1626; g) T. Ball, G. C. Lloyd-Jones, C. A. Russell, *Science* **2012**, *337*, 1644–1648; h) X. C. Cambeiro, T. C. Boorman, P. Lu, I. Larrosa, *Angew. Chem.* **2013**, *125*, 1825–1828; *Angew. Chem. Int. Ed.* **2013**, *52*, 1825–1828.

[4] A. S. K. Hashmi, C. Lothschütz, R. Döpp, M. Rudolph, T. D. Ramamurthi, F. Rominger, *Angew. Chem.* **2009**, *121*, 8392–8395; *Angew. Chem. Int. Ed.* **2009**, *48*, 8243–8246.

[5] a) Y. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc.* **2009**, *131*, 18022–18023; b) Y. Shi, S. D. Ramgren, S. A. Blum, *Organometallics* **2009**, *28*, 1275–1277.

[6] For palladium-catalyzed reactions employing stoichiometric amounts of organogold species see the two reviews: a) P. Garcia, M. Malacria, C. Aubert, V. Gandon, L. Fensterbank, *ChemCatChem* **2010**, *2*, 493–497; b) S. A. Blum, J. J. Hirner, Y. Shi, *Acc. Chem. Res.* **2011**, *44*, 603–613, and: c) A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 1307–1314; d) M. Peña-López, M. Ayán-Varela, L. A. Sarandeses, J. Pérez Sestelo, *Chem. Eur. J.* **2010**, *16*, 9905–9909; e) D. Weber, M. R. Gagné, *Chem. Commun.* **2011**, *47*, 5172–5174; f) K. E. Roth, S. A. Blum, *Organometallics* **2011**, *30*, 4811–4813.

[7] Y. Shi, S. A. Blum, *Organometallics* **2011**, *30*, 1776–1779.

[8] J. J. Hirner, S. A. Blum, *Organometallics* **2011**, *30*, 1299–1302.

[9] P. Cornell, Y. Shi, S. A. Blum, *Organometallics* **2012**, *31*, 5990–5993.

[10] L. Molinari, A. S. K. Hashmi, *Organometallics* **2011**, *30*, 3457–3460.

[11] For a more complete picture of various Au−M transmetalations, see: a) R. J. Cross, M. F. Davidson, A. J. McLennan, *J. Organomet. Chem.* **1984**, *265*, c37–c39; b) R. J. Cross, M. F. Davidson, *J. Chem. Soc. Dalton Trans.* **1986**, 411–414; c) M. Contel, M. Stol, M. A. Casado, G. P. M. van Klink, D. D. Ellis, A. L. Spek, G. van Koten, *Organometallics* **2002**, *21*, 4556–4559; d) M. I. Bruce, M. E. Smith, N. N. Zaitseva, B. W. Skelton, A. H. White, *J. Organomet. Chem.* **2003**, *670*, 170–177; e) A. B. Antonova, M. I. Bruce, B. G. Ellis, M. Gaudio, P. A. Humphrey, M. Jevric, G. Melino, B. K. Nicholson, G. J. Perkins, B. W. Skelton, B. Stapleton, A. H. White, N. N. Zaitseva, *Chem. Commun.* **2004**, *8*, 960–961; f) M. Ferrer, L. Rodríguez, O. Rossell, J. C. Lima, P. Gómez-Sal, A. Martín, *Organometallics* **2004**, *23*, 5096–5099; g) M. I. Bruce, P. A. Humphrey, G. Melino, B. W. Skelton, A. H. White, N. Zaitseva, *Inorg. Chim. Acta* **2005**, *358*, 1453–1468; h) M. Robitzer, I. Bouamaed, C. Sirlin, P. A. Chase, G. van Koten, M. Pfeffer, *Organometallics* **2005**, *24*, 1756–1761; i) C.-L. Chan, K.-L. Cheung, W. H. Lam, E. Chung-Chin Cheng, N. Zhu, S. W.-K. Choi, V. W.-W. Yam, *Chem. Asian J.* **2006**, *1*, 273–286; j) M. Stol, D. J. M. Snelders, H. Kooijman, A. L. Spek, G. P. M. van Klink, G. van Koten, *Dalton Trans.* **2007**, 2589–2593.

[12] For representative reviews on gold catalysis, see: a) A. S. K. Hashmi, G. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; d) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; e) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; f) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; g) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; h) J. Xiao, X. Li, *Angew. Chem.* **2011**, *123*, 7364–7375; *Angew. Chem. Int. Ed.* **2011**, *50*, 7226–7236; i) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; j) *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), Wiley-VCH, Weinheim **2012**.

[13] a) L. A. Jones, S. Sanz, M. Laguna, *Catal. Today* **2007**, *122*, 403–406; b) B. Panda, T. K. Sarkar, *Chem. Commun.* **2010**, *46*, 3131–3133; d) B. Panda, T. K. Sarkar, *Tetrahedron Lett.* **2010**, *51*, 301–305.

[14] a) Y. Shi, S. M. Peterson, W. W. Haberaecker III, S. A. Blum, *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169; b) J. J. Hirner, K. E. Roth, Y. Shi, S. A. Blum, *Organometallics* **2012**, *31*, 6843–6850.

[15] S. Ma, Z. Yu, *J. Org. Chem.* **2003**, *68*, 6149–6152.

[16] a) M. H. Pérez-Temprano, J. A. Casares, Á. R. de Lera, R. Álvarez, P. Espinet, *Angew. Chem.* **2012**, *124*, 5001–5004; *Angew. Chem. Int. Ed.* **2012**, *51*, 4917–4920; b) J. delPozo, D. Carrasco, M. H. Pérez-Temprano, M. García-Melchor, R. Álvarez, J. A. Casares, P. Espinet, *Angew. Chem.* **2012**, *125*, 2245–2249; *Angew. Chem. Int. Ed.* **2013**, *52*, 2189–2193.

[17] For an overview, see: a) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; b) L. P. Liu, G. B. Hammond, *Chem. Soc. Rev.* **2012**, *41*, 3129–3139.

[18] M. Pernpointner, A. S. K. Hashmi, *J. Chem. Theory Comput.* **2009**, *5*, 2717–2725; b) M. Lein, M. Rudolph, S. K. Hashmi, P. Schwerdtfeger, *Organometallics* **2010**, *29*, 2206–2210; c) A. S. K. Hashmi, M. Pernpointner, M. M. Hansmann, *Faraday Discuss.* **2011**, *152*, 179–184.

[19] Gaussian 03, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.

[20] a) P. Hohenberg, W. Kohn, *Phys. Rev. B* **1964**, *136*, B864–B871; b) W. Kohn, L. J. Sham, *Phys. Rev.* **1965**, *140*, A1133–A1138.

[21] D. Figgen, G. Rauhut, M. Dolg, H. Stoll, *Chem. Phys.* **2005**, *311*, 227–244.

[22] K. A. Peterson, D. Figgen, M. Dolg, H. Stoll, *J. Chem. Phys.* **2007**, *126*, 124101.

[23] P. J. Stephens, J. F. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[24] a) C. Peng, H. B. Schlegel, *Isr. J. Chem.* **1993**, *33*, 449–454; b) C. Peng, P. Y. Ayala, H. B. Schlegel, M. J. Frisch, *J. Comput. Chem.* **1996**, *17*, 49–56.

[25] a) K. Fukui, *Acc. Chem. Soc.* **1981**, *12*, 363–368; b) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154–2161; c) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.

[26] No large solvent effects could be detected experimentally; see ref. [4], and, as we could not detect large dipole moments in our calculations, we excluded a special calculation of solvent effects.

[27] a) D. F. McMillen, D. M. Golden, *Annu. Rev. Phys. Chem.* **1982**, *33*, 493–532; b) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047–1062.

[28] J. R. Brown, P. Schwerdtfeger, D. Schröder, H. Schwarz, *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 485–492.

[29] We made a similar observation of no further improvement changing from pVDZ to pVTZ, see: R. Döpp, C. Lothschütz, T. Wurm, M. Pernpointner, S. Keller, F. Rominger, A. S. K. Hashmi, *Organometallics* **2011**, *30*, 5894–5903.

[30] For some theoretical and experimental studies on Au−X bond-dissociation energies without phosphine ligands; see: a) C. Puzzarini, K. A. Peterson, *Chem. Phys.* **2005**, *311*, 177–186; b) M. Guichemerre, G. Chambaud, H. Stoll, *Chem. Phys.* **2002**, *280*, 71–102; c) H. Schwarz, *Angew. Chem.* **2003**, *115*, 4580–4593; *Angew. Chem. Int. Ed.* **2003**, *42*, 4442–4454.

[31] A full calculation with triphenylphosphane was not feasible due to the system size, but a modeling with PMe$_3$ is a justified approach, see: C. M. Krauter, A. S. K. Hashmi, M. Pernpointner, *ChemCatChem* **2010**, *2*, 1226–1230.

[32] Espinet et al. demonstrated that a *cis*–*trans*-isomerization process in the coordination sphere of Pd^{II} can be efficiently catalyzed by using Au^{I} complexes, see: A. L. Casado, P. Espinet, *Organometallics* **1998**, *17*, 3677–3683. We also calculated the transmetalation process starting from the corresponding *cis*-[PdXPhL$_2$] complex, which gave no deeper insight and decided for the reason of clarity not to include this.

[33] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595; b) C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe, L. Ricard, *J. Am. Chem. Soc.* **2003**, *125*, 4212; c) R. Alvarez, O. N. Faza, A. R. D. Lera, D. J. Cardenas, *Adv. Synth. Catal.* **2007**, *349*, 887–906; d) A. Nova, G. Ujaque, F. Maseras, A. Lledós, P. Espinet, *J. Am. Chem. Soc.* **2006**, *128*, 14571–14578; e) P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 4808–4839; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734; f) A. L. Casado, P. Espinet, *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985; g) A. L. Casado, P. Espinet, A. M. Gallego, *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782.

[34] For an overview, see: a) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473–2506; *Angew. Chem. Int. Ed. Engl.* **1995**, *33*, 2379–2411; b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[35] R. Martin, S. L. Buchwald, *Acc. Chem. Soc.* **2008**, *41*, 1461–1473.

[36] a) A. A. C. Braga, N. H. Morgon, G. Ujaque, F. Maseras, *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307; b) C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2011**, *17*, 2492–2503.

[37] For studies analyzing the dependence of the ligand system on the oxidative addition, see: a) S. Niu, M. B. Hall, *Chem. Rev.* **2000**, *100*,

353–406; b) W. A. Herrmann, C. P. Reisinger, M. Spiegler, *J. Organomet. Chem.* **1998**, *557*, 93–96; c) E. Zuidema, P. W. N. M. van Leeuwen, C. Bo, *Organometallics* **2005**, *24*, 3703–3710.

[38] Recently, Gagne et al. were also unable to find suitable reaction conditions for the cross-coupling of toluene triflate (TolOTf) with a variety of palladium catalysts and observed redox incompatibilities of the Pd/Au system, see ref. [6e].

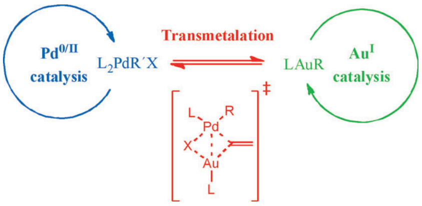
[39] For a minireview on the role of chlorides in catalytic reactions, see: a) A. Jutand, *Appl. Organomet. Chem.* **2004**, *18*, 574–582; b) A. Jutand, A. Mosleh, *Organometallics* **1995**, *14*, 1810–1817.

[40] a) C. Amatore, M. Azzabi, A. Jutand, *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384; b) C. Amatore, A. Jutand, A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531–9541; for an overview, see: c) C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314–321.

[41] a) M.-E. Moret, D. Serra, A. Bach, P. Chen, *Angew. Chem.* **2010**, *122*, 2935–2939; *Angew. Chem. Int. Ed.* **2010**, *49*, 2873–2877; b) D. Serra, M.-E. Moret, P. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8914–8926.

Received: May 14, 2013

A helping hand: For the transmetalation from gold(I) to palladium(II), halide ions play a crucial role (see scheme). Without the formation of a strong gold(I)–halogen bond (e.g., with sulfonate), the transmetalation does not proceed.



Transmetalation

M. M. Hansmann, M. Pernpointner,*
R. Döpp, A. S. K. Hashmi* . ■■■■–■■■■

A Theoretical DFT-Based and Experimental Study of the Transmetalation Step in Au/Pd-Mediated Cross-Coupling Reactions