Cross-Coupling

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Gold and Palladium Combined for Cross-Coupling**

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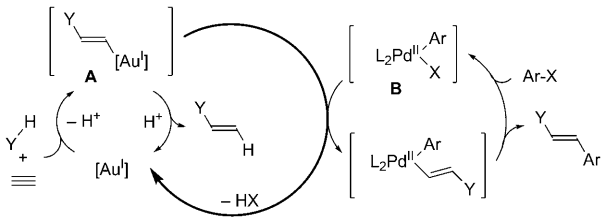
The use of gold catalysts as highly active tools for efficient and atom-economic transformations continues to grow exponentially.[1] In contrast to other transition metals, the most significant limitation of homogeneous gold catalysts seems to be the inferior ability of gold to change oxidation states during catalytic cycles. Of the few reported homogeneous gold-catalyzed coupling reactions in which changes in oxidation states in catalytic cycles are presumed, they are all accomplished at elevated temperatures wherein heterogeneous catalysis should at least be considered.[2] One approach to broadening the scope of gold-catalyzed coupling reactions was accomplished by the use of external stoichiometric oxidants instead of oxidation by the substrate.[3,4] Whereas recently only symmetric molecules could be synthesized by the oxidative dimerization of gold(III) intermediates, Zhang and co-workers reported an impressive oxidative cross-coupling reaction using Selectfluor as reoxidizing reagent.[5]

In our opinion, there is another option to extend the scope of homogeneous gold chemistry: the transmetalation of the in situ generated organogold species **A** to other transition metals such as palladium species **B** (Scheme 1). In these reactions strong stoichiometric oxidizing reagents could be avoided, and the reluctance of the gold species to undergo an oxidation state change could become an advantage as the orthogonal reactivity of the two metals could guarantee highly selective reactions. Our initial experiments to achieve a double catalytic conversion gave only low yields, potentially caused by the ligand exchange processes between the two different metal centers. Therefore we decided to turn to transmetalation experiments using stoichiometric amounts organogold compounds to simplify the reaction conditions. To the best of our knowledge, a general study of the transmetalation abilities of organogold compounds with catalytic amounts of palladium is lacking. So far there are only few examples for transmetalation and gold.[6]



Scheme 1. Transmetalation of organogold intermediates.

Herein we present a study of the gold/palladium system by using stoichiometric amounts of organogold compounds and catalytic amounts of palladium complexes in cross-coupling reactions. Our initial foray into the cross-coupling of organogold intermediates began with an assessment of palladium catalysts **1–7** (Figure 1)[7] for the model reaction of iodobenzene and triphenylphosphine vinyl gold **8a**. Of the different

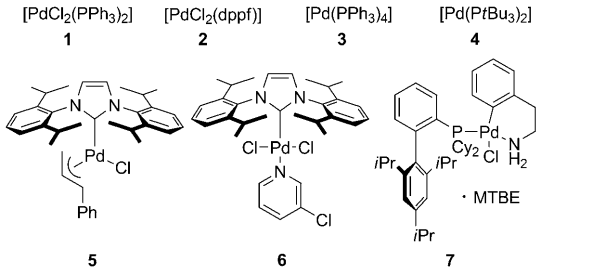


Figure 1. Palladium catalysts. Cy = cyclohexyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, MTBE = *tert*-butylmetyl ether.

catalysts used, **2** delivered the highest conversion rates (Figure 2). The positive effect of a bidentate ligand on the palladium lies in the prevention of ligand exchange reactions between the two metal centers, as these are not chelating ligands for gold(I) through a linear coordination geometry. Switching to the use of the monodentate N-hetereocyclic carbene (NHC) complex **5** delivered only poor results, even after several days. Encouraged by the results obtained with the phosphane ligands, we performed a solvent screening using the optimized catalyst system (**2**). Changing the type of solvent seemed to have only a minor impact on transmetalation, the efficiency of which decreased in the following order: $CH_3CN \approx DMF > dioxane \approx toluene > THF > Et_2O$. We did not use protic solvents so as to avoid possible problems caused by protodeauration. To gain insight into the variability of the cross-coupling, we expanded our procedure to different organogold species as well as different aryl halides (Table 1).

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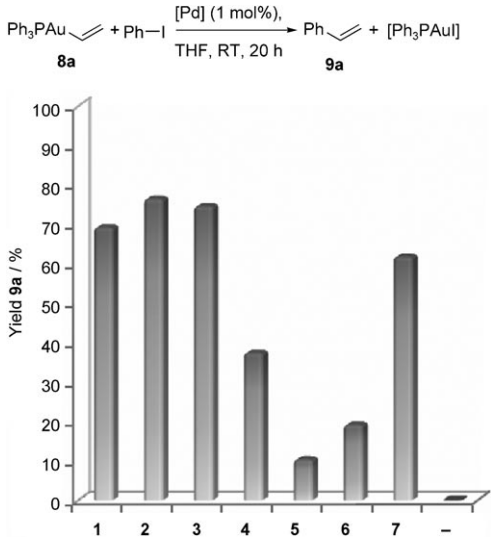


Figure 2. Catalyst screening.

For a series of different aryl halides and triphenylphosphinevinylgold (Table 1, entries 1–5), it turned out that the use of electron-rich substrates (Table 1, entry 4) led to lower yields, thus indicating that the oxidative addition step might be rate determining. By using the diastereomerically pure *trans*-styrene gold compound **8 f** (Table 1, entry 6), complete conservation of double bond geometry was observed. Comparable results were achieved by the use of triphenylphosphine alkynylgold compounds (Table 1, entries 7 and 8), as well as arylgold compounds (Table 1, entries 9–12). In most cases our yields were lower when compared to those of existing cross-coupling methods, however in a number of cases our yields were higher.[9]

Usually organogold compounds were synthesized by transmetalation reactions from electropositive metals such as lithium, magnesium, or boron;[10] recently, Hammond and co-workers were able to isolate a stable vinylgold compound as the product of an allene cycloisomerization reaction with stoichiometric amounts of gold.[11] Naturally, we were excited to test these substrates for a possible coupling reaction. On the basis of the unprecedented thermal stability of the gold furanones used (Table 1, entries 13–19) we were able to perform these transformations at elevated temperatures. Under these conditions unactivated aryl halides (Table 1, entries 16–18) gave moderate to good yields. To prove the potential of the reaction, we carried out the transformation on a 2 mmol scale (Table 1, entry 15) with an excellent yield. The structure of the product **9 n** was confirmed by X-ray crystallographic analysis (Figure 3).[8] The latter example might clarify the scope of the procedure developed.

By combining the high reactivity of gold for cycloisomerization reactions together with its transmetalation ability, it is possible to generate complex organic compounds which could not be easily prepared by any other procedure. Even though this procedure still demands stoichiometric amounts of the gold compound, a nearly quantitative reisolation (> 99 %) of the gold as triphenylphosphine gold iodide, should make this procedure attractive for preparative use in organic synthesis.

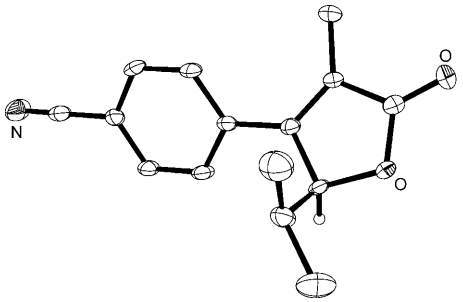
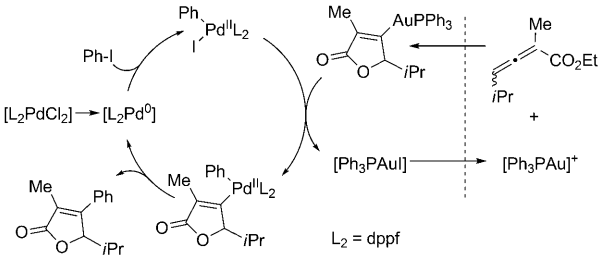


Figure 3. Molecular structure of coupling product **9 n**. Thermal ellipsoids shown at 50% probability.

Reactivation of the gold halide with silver tosylate allowed us to run a second cycle of this transformation (Scheme 2). As in other cross-couplings, the in situ reduction of Pd^{II} precatalysts, also shown in Scheme 2, probably proceeds by a two transmetalation steps and subsequent reductive elimination.

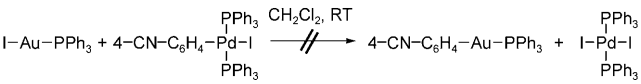


Scheme 2. Reaction pathway and re-activation of gold(I).

A limitation of this transformation is the use of sterically hindered aryl halides. By using *o*,*o*-disubstituted iodobenzene, only the starting organogold compound could be isolated (Table 1, entry 17).

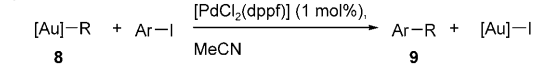
To investigate the ligand dependency of the transmetalation step, we introduced NHCs as well as noncyclic amino carbenes (NCAC) as ligands on the organogold compounds (Table 2). In the case of the mesityl compounds (Table 2, entry 1 and 2) the conformationally more flexible NCAC ligand delivered a moderate yield, whereas only poor conversion was detected in the case of the more sterically shielding NHC ligand at room temperature (Table 2, entry 2). Not surprisingly, decreasing steric bulk at the organogold compound delivered better results (Table 2, entry 3 and 4).

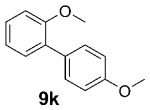
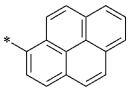
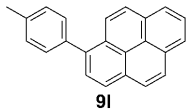
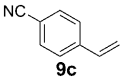
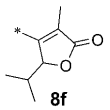
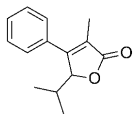
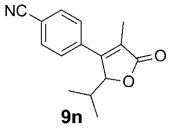
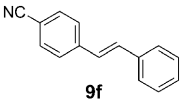
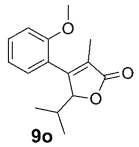
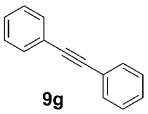
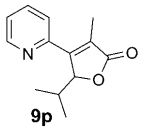
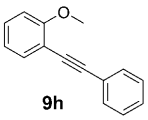
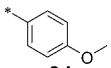
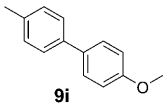
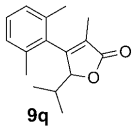
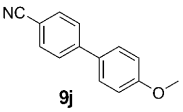
For additional experimental insight into the elemental steps of the gold/palladium system, we used *trans*-[Pd^{II}-$(PPh_3)_2I(4\text{-}CNC_6H_4)$] to probe reversibility of the transmetalation step (Scheme 3). However, the transmetalation turned out to be an irreversible process; as shown by the ^{31}P NMR spectrum which remained unchanged.



Scheme 3. The transmetalation is irreversible.

Table 1: Cross-coupling of organogold compounds.

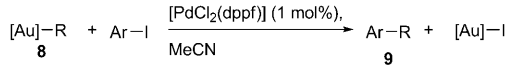


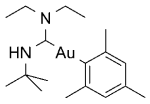
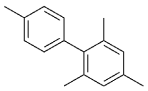
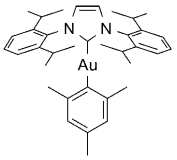
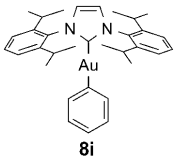
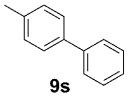
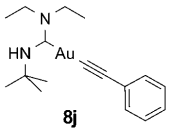
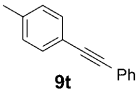
Entry	**8**, R	*t* [h]	Product	Yield [%]	Entry	**8**, R	*t* [h]	Product	Yield [%]
1	 **8a**	24	 **9a**	85[a]	11	**8d**	48	 **9k**	73
2	**8a**	24	 **9b**	18[a]	12	 **8e**	24	 **9l**	73
3	**8a**	24	 **9c**	88[a]	13	 **8f**	4	 **9m**	86
4	**8a**	24	 **9d**	39[a]	14	**8f**	4	 **9n**	91[c]
5[f]	**8a**	24	 **9e**	50[a]	15	**8f**	4	**9n**	95[d]
6	 **8b**	24	 **9f**	54	16	**8f**	4	 **9o**	84
7	 **8c**	24	 **9g**	84	17	**8f**	72	 **9p**	92
8	**8c**	24	 **9h**	46	18[f]	**8f**	72	**9p**	37
9	 **8d**	24	 **9i**	74	19	**8f**	48	 **9q**	0[e]
10	**8d**	24	 **9j**	76[b]					

[a] Yield determined by GC methods; average of two runs. [b] See the Supporting Information for the solid-state structure analysis of **8d**.[8] [c] [Ph_3PAuI] isolated in 94% yield. [d] Reaction carried out on 2 mmol scale. 1.1 Equivalent of 4-iodobenzonitrile; isolated 99% of [Ph_3PAuI]. [e] The starting material, [Ph_3PAuR], was reisolated in 97% yield. [f] Br instead of I.

In conclusion, we have shown that the transmetalation from organogold(I) compounds to palladium is a generally applicable methodology. All the reactions examined could be carried out under very mild reaction conditions with no significant solvent influence. In contrast to other coupling procedures, the addition of any additives was not necessary. Furthermore, the remarkable stability of the gold compounds is worth mentioning. Currently, we are working on a version of this method which is catalytic in both metals by using substrates which having anions with a less pronounced affinity to gold relative to the halides, as well as a potential transmetalation from organogold(III) compounds.

Table 2: Ligand influence on the transmetalation.[a]



Entry	LAuR	Product	Yield [%]
1	 **8g**	 **9r**	32
2	 **8h**	**9r**	2[b]
3	 **8i**	 **9s**	82[b]
4	 **8j**	 **9t**	96

[a] Reaction time was 24 h. [b] Yield was determined by GC methods.

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