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Gold-Catalyzed Cross-Couplings: New Opportunities for C–C Bond Formation

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Cross-coupling is a powerful tool for the rapid construction of highly valuable compounds. In this area of chemical transformations, new catalysts have recently emerged. Combining both a π -Lewis acid character and interesting redox properties, gold has proven to be an expedient choice for mediating such transformations. Recent developments in the use of gold to

mediate a variety of C–C coupling reactions are summarized, including Suzuki and Sonogashira cross-coupling reactions, as well as the development of tandem processes and the combination of gold with palladium to enable C–C bond formation via transmetalation.

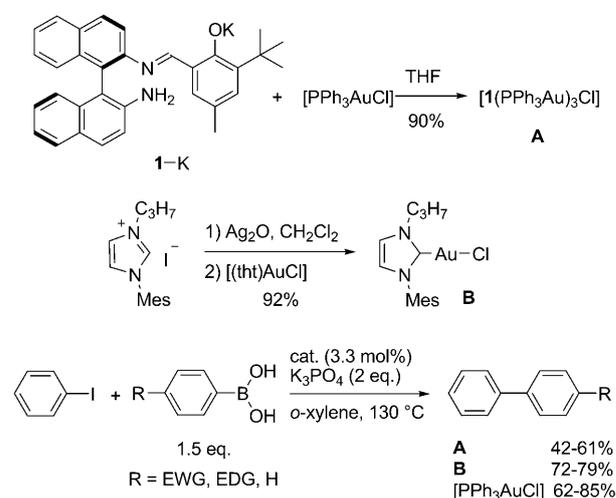
Introduction

Transition metal catalysis is one of the best tools for the development of green chemistry.^[1] Among the catalysts that allow selective transformations, gold has proven in recent times to be a metal of choice, notably concerning the activation of multiple C–C bonds.^[2] Well-known for their π Lewis acid character, gold salts have lately been shown to exhibit other notable qualities. Gold species can also catalyze the formation of C–C bonds in cross-coupling reactions. Herein we summarize relatively recent progress made in gold-catalyzed C–C cross-coupling strategies.

Suzuki Cross-Coupling Reactions

The potential of gold catalysts for Suzuki coupling reactions was first reported by Tsukuda^[3] and then fully investigated by Corma and co-workers,^[4] who carried out efficient homocoupling of phenylboronic acids using supported or soluble gold salts. The complexes were all based on Au^{III} supported on ceria particles^[4a] or derived from Schiff-base ligands for homogeneous studies.^[4b] These promising results encouraged an in-depth investigation into conditions for cross-coupling reactions. For that purpose, Corma and co-workers turned their attention to Au^I sources. Indeed, Au^I has the same d¹⁰ electronic configuration as Pd⁰, which is the active species in most Suzuki cross-coupling reactions.^[5] The use of the Au^I Schiff-base complex **A** yielded nonsymmetrical biaryls in good yields (Scheme 1), whereas the reaction catalyzed by a Au^{III} complex of the same ligand furnished the homocoupling product only.^[5a–c] Of other types of complexes investigated, commercially available [PPh₃AuCl] and complex **B**, bearing an unsymmetrical N-heterocyclic carbene(NHC) ligand (Scheme 1), also proved very efficient for promoting cross-coupling of aryl iodides.^[5d]

Corma and co-workers also modified the catalytic system involving an NHC to enable its attachment to a support, in order to study its behavior as a heterogeneous catalyst.^[5e] Anchoring

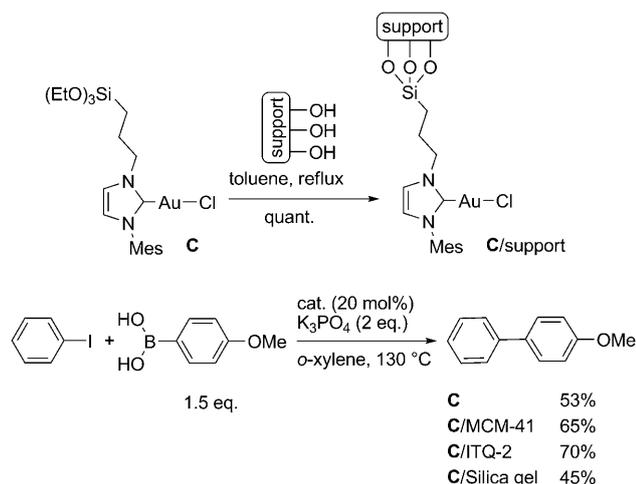


Scheme 1. Au^I-catalyzed Suzuki cross-coupling reactions; tht = tetrahydrothiophene.

was facilitated by functionalizing the NHC ligand with a 3-(triethoxysilyl)propyl tether to form the gold complex **C** (Scheme 2). Three different supports were investigated: An ordered mesoporous silica (MCM-41), a delaminated zeolite (ITQ-2), and silica gel. The experiments with the silica gel-supported catalyst showed a loss of catalytic activity with respect to the homogeneous NHC catalyst, whereas attachment to the other supports led to an increased activity (Scheme 2). Moreover, four consecutive recycling experiments were performed

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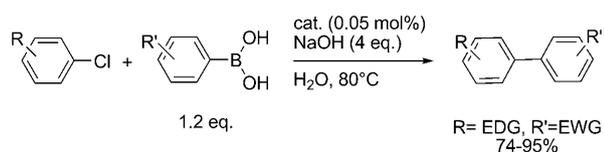
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Scheme 2. Suzuki cross-coupling catalyzed by supported Au^I carbene complexes.

with **C/MCM-41**, showing no significant deactivation of the catalyst.

Guo and co-workers showed that gold nanoparticles were also able to catalyze Suzuki cross-couplings in water.^[6] Formation of the gold nanoparticles was accomplished by a redox reaction between $HAuCl_4$ and 2-aminothiophenol, furnishing poly(2-aminothiophenol) (PATP), which can act as capping agent. The stable PATP–gold nanoparticles exhibited an excellent catalytic activity towards Suzuki cross-coupling. Only 0.05 mol% of catalyst was required for the coupling of traditionally sluggishly reactive aryl chlorides (Scheme 3). A study of the recyclability of the catalyst by simple filtration also showed no loss of activity after six runs.

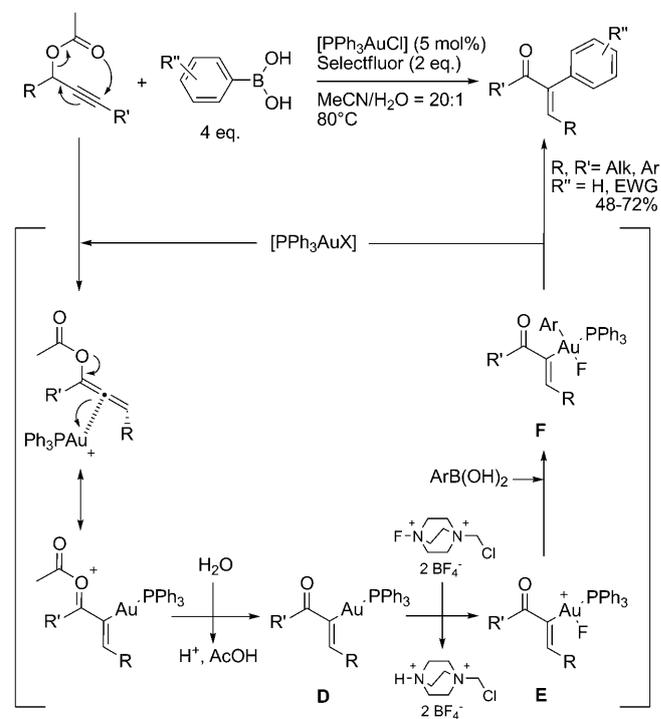


Scheme 3. Suzuki cross-coupling reactions catalyzed by PATP-capped gold nanoparticles.

It should also be mentioned that biaryls have also been synthesized by direct C–H arylation of pyrazine and pyridine with aryl bromides, using a combination of a gold(I) complex and potassium *tert*-butoxide. However, the exact role of gold in this reaction is not clear.^[7]

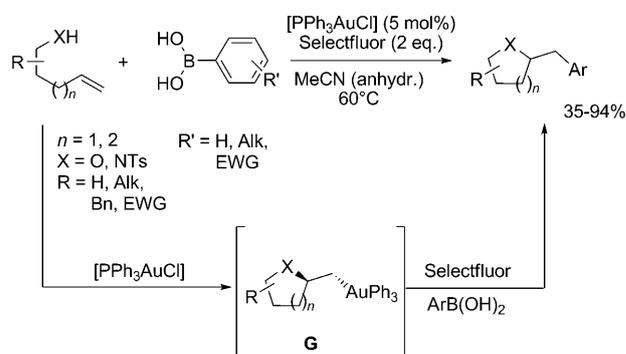
Taking advantage of the well-known ability of gold to mediate 3,3-rearrangement of propargyl acetates into allenyl acetates,^[8] Zhang and co-workers recently reported an expedient type of cross-coupling.^[9] Under oxidative conditions, propargyl acetates and boronic acids gave rise to α -aryl α,β -enones in moderate to good yields. The authors proposed a Au^I/Au^{III} catalytic mechanism, which proceeds as follows: After 3,3-rearrangement of the acetate, the resulting intermediate is

hydrolyzed into vinyl–gold species **D**, which is subsequently oxidized by selectfluor (1-chloromethyl-4-fluorodiazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)) to furnish the Au^{III} species **E**. The latter undergoes transmetalation with boronic acid to give the diorganogold intermediate **F** (Scheme 4). Reductive elimination regenerates the active Au^I species and delivers the cross-coupling product. Notably, *E* selectivity is total.



Scheme 4. Au^I -catalyzed tandem triple-bond activation–Suzuki cross-coupling.

The same group later reported another synthetic application of the $[PPh_3AuCl]$ /selectfluor system in the oxidative carboheterofunctionalization of alkenes (Scheme 5), which relies on the conversion of $C(sp^3)–Au$ bonds into $C(sp^3)–Ar$ bonds.^[10] In this case, activation of the double bond of the substrate by Au^I is followed by intramolecular nucleophilic attack. The resulting



Scheme 5. Au^I -catalyzed oxidative carboheterofunctionalization of alkenes.

alkyl–gold species **G** is then efficiently cross-coupled with boronic acids under oxidative conditions.

Sonogashira Cross-Coupling Reactions

In parallel with their work on Suzuki cross-couplings, Corma and co-workers evaluated their catalysts for Sonogashira reactions.^[5b,e,11,12] As expected, the catalysts afforded the desired product in moderate to good yields. It is important to note that the commercially available catalyst [PPh₃AuCl], provided the best efficiency (with **A**, 20 mol% of catalyst gives 60 mol% of gold; Table 1). Once again, the use of Au^{III} gave rise only to dimerization of the starting alkyne.

Table 1. Gold-catalyzed Sonogashira cross-coupling yields with various homogeneous and supported catalysts.

| R | R' | A | C | C/MCM-41 | [PPh ₃ AuCl] |
|--------------------|---|--------------------|--------------------|--------------------|-------------------------|
| H | Ph | 54% ^[a] | 17% ^[a] | 34% ^[a] | 35% ^[a] |
| H | CH ₂ CH(Ac) ₂ | 10% ^[a] | 15% ^[a] | 10% ^[a] | 40% ^[a] |
| H | <i>n</i> -C ₁₀ H ₁₇ | 10% ^[b] | – | – | 97% ^[b] |
| CO ₂ Et | Ph | 10% ^[b] | – | – | 95% ^[b] |

[a] *t* = 24 h; [b] *t* = 48 h.

The catalytic system developed by da Silva and co-workers allowed the reaction time to be lowered to 1–3.5 h.^[13] Using silica-supported gold nanoparticles under microwave irradiation rendered the copper-free Sonogashira reaction truly efficient with a catalyst loading as low as 3 mol%. The reaction also proved compatible with aryl bromides and substrates bearing electron-donating substituents, albeit with longer reaction times (Table 2).

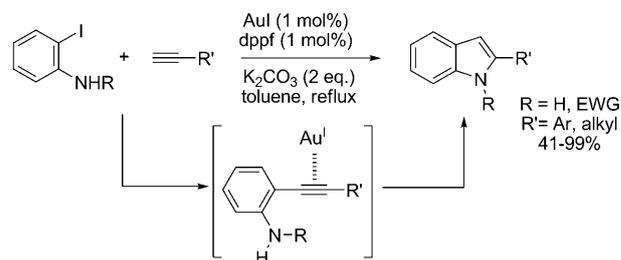
Table 2. Microwave-promoted gold-nanoparticles-catalyzed Sonogashira Cross-Coupling yields.

| R | R' = Ph | R' = <i>n</i> -C ₆ H ₁₃ |
|-----------------|--------------------|---|
| H | 87% ^[a] | 66% ^[a] |
| NO ₂ | 84% ^[a] | 78% ^[a] |
| OMe | 56% ^[b] | 59% ^[b] |

[a] *t* = 1 h, [b] *t* = 3.5 h.

In 2008, the use of a small amount of readily available catalyst enabled Wang and co-workers to develop an efficient cross-coupling procedure.^[14] With only 1 mol% of gold(I) iodide and exploiting the well-established gold-mediated

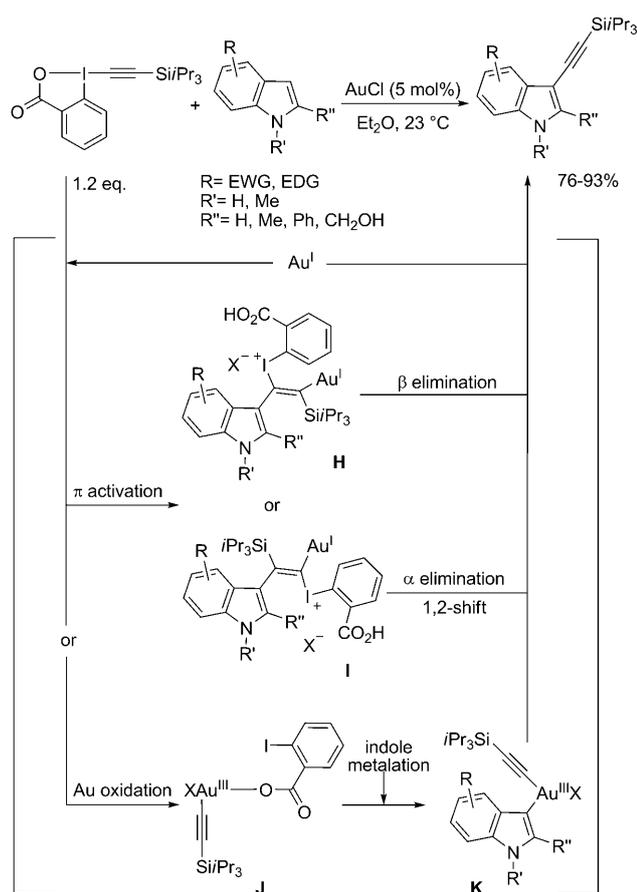
triple-bond activation toward nucleophilic attack, several indoles were prepared by a tandem Au^I-catalyzed coupling–cyclization strategy (Scheme 6).



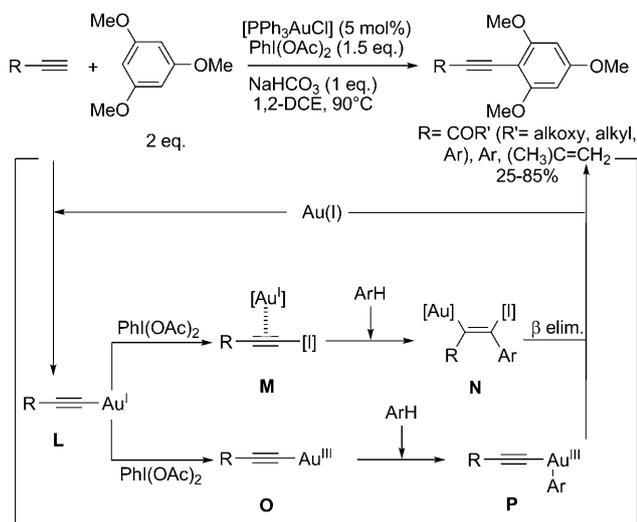
Scheme 6. Au^I-catalyzed tandem coupling–cyclization reactions of alkynes with *o*-iodoanilines; dppe = 1,1'-bis(diphenylphosphino)ferrocene.

Indoles can also be efficiently functionalized through gold(I) catalysis. By using catalytic amounts of AuCl, Waser and co-workers reported a convenient method for the alkylation of pyrroles and indoles.^[15] This method is highly attractive since both electron-withdrawing and -donating groups are very well tolerated. Notably, even the presence of a halogen atom (R = I, Br) at the pyrrole ring does not interfere. Two mechanistic pathways were proposed for this reaction (Scheme 7). The first involves the addition of the indole to the activated triple bond of the starting hypervalent iodine derivative, furnishing vinyl–gold intermediates **H** or **I**. The end of the catalytic cycle comprises a β elimination or an α elimination/1,2-shift sequence. Another plausible pathway consists of Au^I oxidation by the starting hypervalent iodine derivative yielding **J**, which, after indole metalation, affords gold(III) acetylide **K**. Subsequently, reductive elimination gives the desired product (Scheme 7).

In 2001, an efficient coupling between aryl–gold(III) species and phenylacetylene was reported by Fuchita.^[16] This transformation was particularly attractive since no halogenated partner was required, either in the formation of the aryl–gold derivative, or during its coupling with a terminal alkyne. Taking into account that this method requires a stoichiometric amount of gold, Nevado and co-workers developed a catalytic version using 5 mol% of [PPh₃AuCl].^[17] This approach also appears quite attractive, since electron-rich aromatics, which traditionally exhibit low reactivity, undergo straightforward arene alkylation under these new conditions (Scheme 8). As for the alkylation of indoles (Scheme 7), two reaction pathways can be envisioned.^[15] After formation of gold(I) acetylide **L**, the first mechanism proposes that reaction with PhI(OAc)₂ furnishes the electrophilic alkynyl–iodonium complex **M**, to which gold-mediated aromatic addition affords vinyl–gold intermediate **N**. β-Elimination of the active catalytic species from **N** then yields the arylated alkyne. An alternative rationale involves a Au^I/Au^{III} catalytic cycle. After formation of gold(I) acetylide **L**, oxidation by PhI(OAc)₂ affords gold(III) acetylide **O**. The next step is arene auration, giving rise to intermediate **P**, which, after reductive elimination, generates the ethynylated adduct and the active catalytic species.



Scheme 7. Au^I-catalyzed alkylation of indoles.

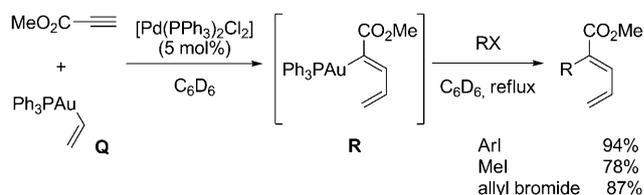


Scheme 8. Au^I-catalyzed ethynylation of electron-rich arenes; DCE = dichloroethane.

Gold and Palladium Synergy

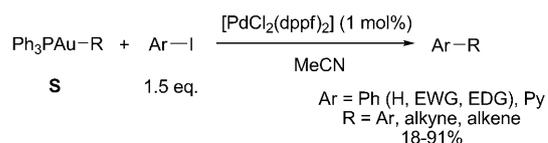
Recently, selective methods for C–C bond formation based on gold/palladium transmetalation have emerged.^[18,19] Blum and

co-workers reported C(sp²)–Ar, and C(sp²)–C(sp³) bond formations in a one-pot carboauration/functionalization starting from vinyl–gold triphenylphosphine **Q**. In the presence of 5 mol% of [Pd(PPh₃)₂Cl₂], treatment of a terminal alkyne afforded carboaurated intermediate **R**. By employing a suitable electrophile, upon palladium catalysis, the latter could be converted into di- or trisubstituted olefins with excellent regio- and diastereoselectivity (Scheme 9).^[20]



Scheme 9. One-pot carboauration–functionalization.

Hashmi and co-workers reported a related procedure. By using 1 mol% of [PdCl₂(dppf)], aryl iodides were coupled with a wide variety of organogold compounds **S** to form Ar–C(sp²), Ar–C(sp) and Ar–Ar carbon–carbon bonds in good yields (Scheme 10).^[21]

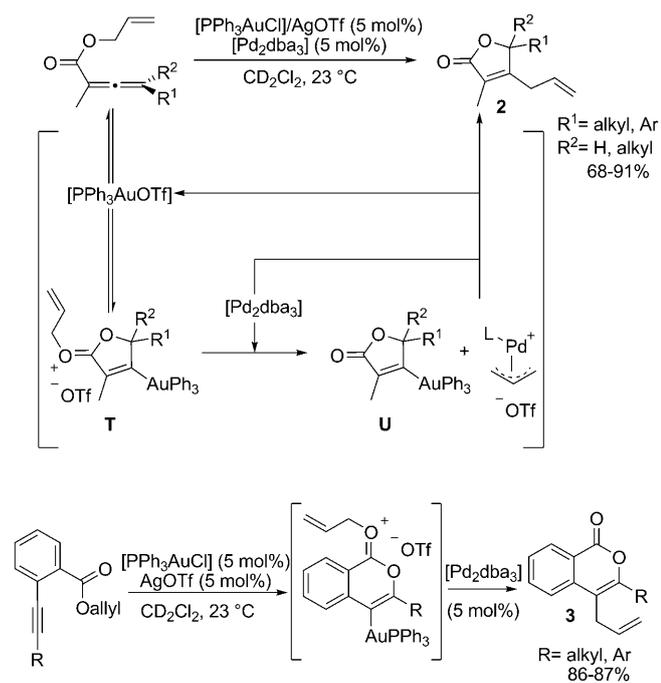


Scheme 10. Cross-coupling of organogold compounds with aryl iodide.

With these results in hand, reactions were developed whereby both metals were used in catalytic amounts. A procedure reported by Blum and co-workers allows the preparation of functionalized butenolides **2** and isocoumarins **3** in very good yields (Scheme 11).^[22] After formation of the allyl oxonium intermediate **T**, generated through Au^I catalysis, Pd⁰-catalyzed deallylation produces the neutral vinyl–gold species **U** alongside a π -allyl Pd^{II} complex. The last step of the proposed catalytic cycle is a C–C bond-forming reductive elimination that regenerates both gold and palladium active species.

Conclusions

Gold has recently been shown to have interesting properties concerning cross-coupling reactions. Gold is not only one more alternative to palladium, but also allows unprecedented chemoselectivity. For instance, the possibilities for tandem cross-coupling–triple-bond activation, copper-free Sonogashira reactions, and the formation of various types of C–C bond demonstrate the potential of gold for cross-couplings. Moreover, the combination of gold and palladium has provided access to new synthetic opportunities. Through the early examples reported here, one can expect impressive develop-



Scheme 11. Synthesis of butenolides and isocoumarins by gold–palladium dual catalysis; dba = *trans,trans*-dibenzylideneacetone.

ments. Indeed, for several of the reported reactions, two potential mechanistic pathways are possible: a $\text{Au}^{\text{I}}/\text{Au}^{\text{III}}$ redox catalytic system may be involved for Suzuki or Sonogashira cross-couplings,^[9,10,15,17,23] or a vinyl–gold intermediate could result from triple-bond activation. Even if traces of other metals could act as the catalytic species,^[12] and more information regarding the precise nature of the catalytic system would certainly be welcome, the high efficiency of a wide range of the reported results suggests the relevance of gold's application to CC couplings. Thus one can bet that the gold rush is not over.

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Keywords: chemoselectivity • cross-coupling • gold • homogeneous catalysis • supported catalysts

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