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Gold Catalysis

Gold for C–C Coupling Reactions: A Swiss-Army-Knife Catalyst?

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C–C coupling · cross-coupling reactions · gold · homogeneous catalysis · palladium

For organic chemists, the construction of C–C bonds is the most essential aspect of the assembly of molecules. Transition-metal-catalyzed coupling reactions have evolved as one of the key tools for this task. Lately, gold has also emerged as a catalyst for this kind of transformation. Gold, with its special properties as a mild carbophilic π Lewis acid, its ability to insert into C–H bonds, and, as discovered recently, its ability to undergo redox transformations, offers the opportunity to apply all this potent proficiency for the construction of compounds in an efficient and economical way. This Minireview critically presents the C–C coupling reactions enabled by gold catalysts to encourage further research activities in this promising area of oxidation/reduction gold catalysts.

1. Introduction

A plethora of transformations in organic synthesis relies on the use of transition-metal catalysts. Recently, gold catalysts have excelled owing to their unique reactivity as mild π Lewis acids.[1] Since 2008, when we and others could demonstrate the involvement of oxidation/reduction processes of the gold metal, gold catalysts have experienced a second life. Additionally, gold catalysts were shown to be able to insert into C–H bonds.[2] Together, these three reactivity patterns of gold catalysts offer an extremely efficient way to assemble complex molecules. In this respect, the construction of C–C bonds is of special interest. The rather immature oxidation/reduction chemistry of gold catalysts has shown particular potential for C–C bond formation. Although a number of gold-catalyzed C–C bond-forming reactions based on this principle have been reported, the mechanistic details are somewhat vague, if not in some cases erroneous. Are gold catalysts able to promote Sonogashira reactions? What is the oxidation state of the gold catalyst in its active state?

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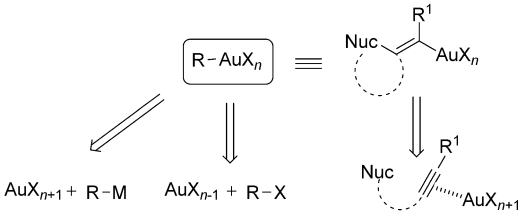
2. General Considerations with Respect to Gold-Catalyzed Coupling Reactions

There exist, in principle, two types of C–C coupling reactions: homocoupling and cross-coupling reactions. Historically, as in the case of the "classical" palladium- and nickel-catalyzed coupling reactions,[3] homocoupling reactions were initially reported for gold catalysis, followed by cross-coupling reactions. The latter can be classified into two different types: "classical" cross-coupling, in which an electrophilic coupling partner (in most cases a halogen compound) is connected with a nucleophilic counterpart (in most cases an organometallic compound), and oxidative coupling, in which two nucleophilic reaction partners (such as tetramethylsilyl derivatives, boronic acids, and C–H bonds) are combined. In all cases, the overall transformation can be broken down into a few elementary steps.

2.1. Creation of the Au–R Species

There are numerous ways to generate an Au–R intermediate (Scheme 1). It can be generated through a substitu-



Scheme 1. Retrosynthetic pathways to Au–R species.

tion/transmetalation reaction with an organometallic species (e.g. a Grignard reagent). Gold catalysts are also known to undergo oxidative addition to R–X bonds, although theoretical studies predict such a process to be highly unfavored.[4] Also, insertion reactions into C–H bonds have been proposed. Finally, probably the most powerful method is the in situ generation of the reactive species owing to the π Lewis acid nature of the gold catalyst, which promotes the addition of a nucleophile to a C=C or C≡C bond with transfer of the gold catalyst to the second carbon atom (Scheme 1). Although intermediates created by all of these methods have been isolated and characterized, it is not always certain whether, for example, a true C–H insertion has taken place. In a number of cases, a Friedel–Crafts-type mechanism is more likely and is supported by mechanistic studies.

2.2. Transmetalation

For the connection of two C atoms, an R–M–R intermediate is proposed in most cases. Such intermediates can be produced by the methods described above, or by transmetalation. Especially when cocatalysts, such as Pd, are in the game, at least one of the coupling partners has to be transferred from the gold to the cocatalyst. Low and coworkers demonstrated that gold–alkynyl complexes undergo efficient transmetalation with a variety of other metals (Scheme 2).[5]

Scheme 2. Transmetalation from gold–alkynyl complexes to other transition-metal alkynyl complexes.

2.3. Reductive Elimination

For the final formation of the desired C–C bond, the two R groups have to be eliminated from the metal: the reductive-elimination step. For gold, this process has been proposed, but it seems to be rather disfavored according to theoretical as well as experimental studies.[6] However, in the first example of an Ullmann-type coupling with Au, Vicente et al. demonstrated that Ar^1–Au^{III}–Ar^2 complexes stabilized by chelating *ortho* substituents undergo reductive elimination to form biaryl compounds upon the addition of a competing ligand (PPh_3).[7]

2.4. Reoxidation of Au^I/Au^{III}

One of the crucial points in the use of a gold catalyst for oxidative coupling is the regeneration of the catalytically active species. In most cases, an Au^I/Au^{III} cycle occurs. Recently, the existence of an Au^{III}/Au^V cycle has also been speculated. Unfortunately, studies on the oxidation/reduction of organometallic gold compounds, especially in organic solvents, are rather scarce.[8] This reality and the variety of oxidants found in the literature for the reoxidization of Au make the analysis of mechanisms involving oxidation-state changes of Au fairly difficult. The oxidation potential is highly dependent on the ligand sphere and also on the counterion. In a few examples, it was shown that the presence of chloride ions is crucial for successful oxidation. In those cases, it is believed that Cl^- is oxidized to Cl_2, which then oxidizes Au.[8c]

Thus, a clear-cut transfer of the established catalytic cycle for coupling reactions with, for example, Pd or Ni to gold-catalyzed processes is not possible. The investigation of reactive intermediates and the fundamental catalytic steps is, therefore, highly desirable and necessary to maximize the undoubtedly high potential of gold catalysts in coupling reactions.

3. Homocoupling Reactions

In the first examples of C–C coupling reactions involving gold, two molecular fragments of the same kind were joined together (see Section 2.3). In these early reactions, the process relied on stoichiometric amounts of the metal. Only selected examples are mentioned explicitly herein, as this area was reviewed earlier.[9]

3.1. Stoichiometric Amounts of Gold

Over ten years ago, Lippert and co-workers described the dimerization of uracil derivatives **1** with a stoichiometric amount of $NaAuCl_4$, including mechanistic details (Scheme 3).[10] Investigations supported the formation of a

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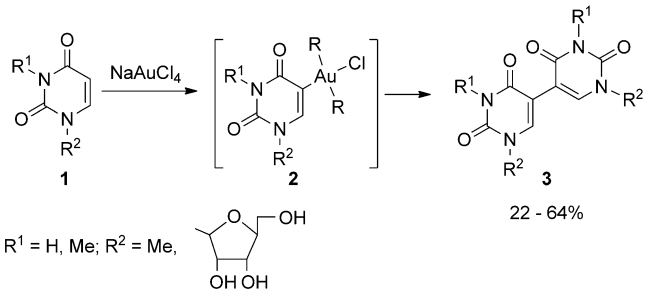
Mathieu Auzias studied chemistry and biochemistry at the University of Montpellier. He completed his MSc in chemistry in July 2004 with a project supervised by Prof. Jean-Louis Montero on the synthesis of glycosyl α-haloepoxyesters, intermediates for the formation of unconventional disaccharides. His PhD research on the development of anticancer ruthenium complexes was supervised by Prof. Georg Süss-Fink. In 2008, he started postdoctoral research with Dr. Hermann Wegner at the University of Basel, where he has developed new gold-catalyzed domino processes.



Scheme 3. Oxidative dimerization of uracil derivatives.

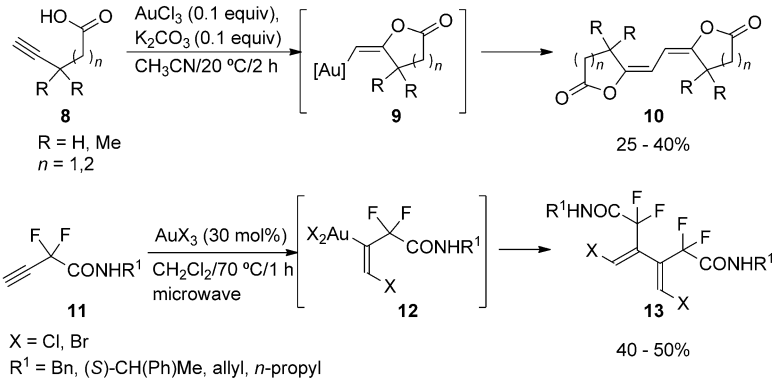
gold intermediate by insertion into a C–H bond, as the corresponding gold(III)–uracil species **2** could be isolated. The subsequent reductive elimination has precedent, as mentioned above. A radical mechanism seems less likely, as no EPR signal was detected during the dimerization process. There have been further reports of oxidative dimerization reactions through similar mechanistic pathways involving C–H insertion,[11] as well as transmetalation reactions with boron compounds.[12]

The first oxidative coupling of an Au–R intermediate, which was generated by the action of gold as a π Lewis acid (cyclization of allenyl carbinols), was observed by Hashmi et al. (Scheme 4).[13] Besides the desired hydrofuran **6** dimer **7** was obtained through an oxidative coupling of the gold intermediate **5** instead of the expected protodeauration step. As no oxidant was present to reoxidize Au^{I} to Au^{III}, the dimerization product **7** was only formed in low yields.

In 2009, Pale and co-workers reported the observation of a similar dimerization upon the treatment of acetylenic acids **8** with a catalytic amount of $AuCl_3$ (Scheme 5, top). An Au–R intermediate **9** was proposed to undergo transmetalation to form an R–Au–R intermediate, reductive elimination from which leads to lactone dimers **10**.[14] A dimerization prior to cyclization could be excluded by separate preparation of the acetylenic dimer. In the same year, Hammond and co-workers reported the similar AuX_3-mediated selective dimerization of difluoropropargyl amides **11** under microwave irradiation (Scheme 5, bottom). The *gem*-difluoro moiety seems to play an essential role in the process, as these alkynes showed unusual behavior.[15]

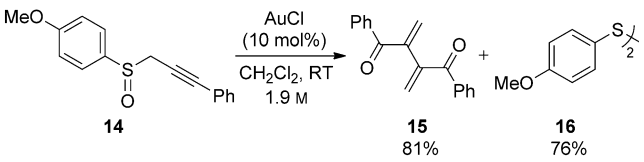
3.2. Catalytic Amounts of Gold

The studies in Section 3.1 clearly indicate that if an efficient oxidant could be identified for the regeneration of the Au^{III} species required for the reductive elimination, the synthetic chemist would have a very efficient catalytic tool for the assembly of complex molecules. The second important aspect is the suppression of protodeauration. In practical terms, the regeneration of the Au^{III} species must be faster than the protodeauration step and the disproportionation of Au^{I} to Au^{0} and Au^{III}.

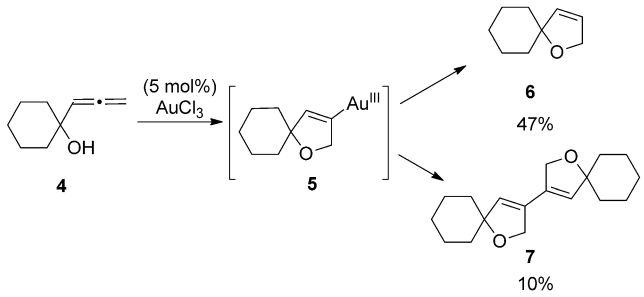


Scheme 5. Oxidative coupling reactions described by Pale and co-workers (top) and Hammond and co-workers (bottom). Bn = benzyl.

In 2007, Shapiro and Toste mentioned the formation of a dimeric product resulting from an oxidative coupling of a Au intermediate.[16] The reoxidation of Au^{I} occurred through dithiane formation (Scheme 6).

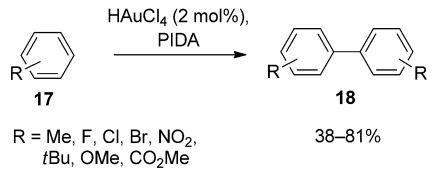


Scheme 6. Dimer formation as a side reaction during the rearrangement of alkynyl sulfoxides.



Scheme 4. Oxidative coupling of an Au^{III}–R intermediate.

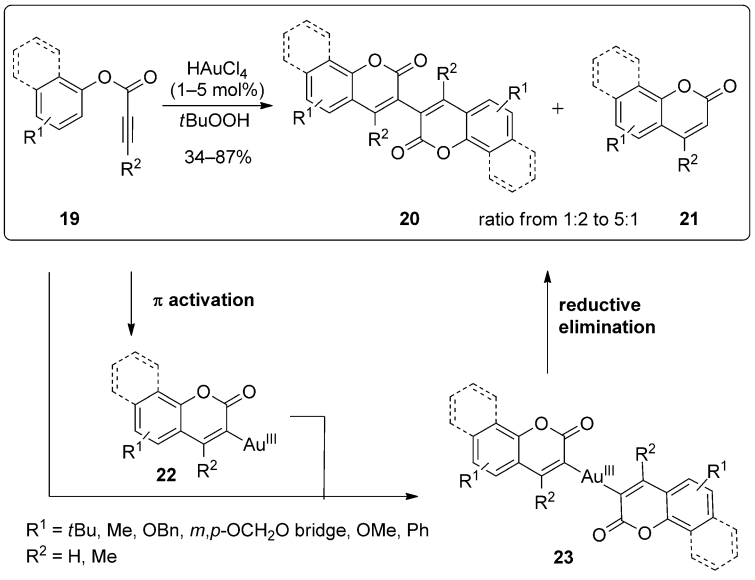
The first report of an oxidative coupling with a catalytic amount of gold and an external oxidant appeared in 2008, when Tse and co-workers described the gold-catalyzed direct oxidative coupling of non-activated arenes **17** (Scheme 7).[17] This very useful transformation occurred in acetic acid, and the gold catalyst ($HAuCl_4$) was reoxidized by (diacetoxyiodo)benzene (PIDA). The reaction was compatible with a wide range of functional groups. Notably, this homocoupling exhibited high preservation of halogen groups. A mechanism involving C–H insertion followed by reductive elimination was proposed: a mechanism similar to that proposed by



Scheme 7. Formation of biaryl compounds by an oxidative coupling with a gold catalyst.

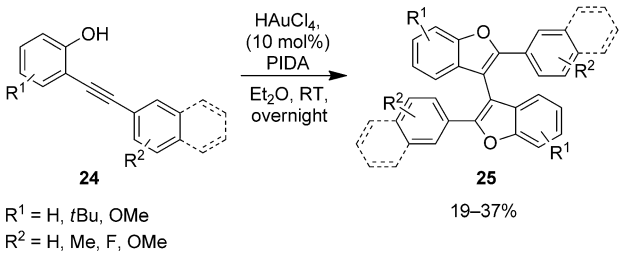
Lippert and co-workers for their dimerization reaction (Section 3.1). However, mechanistic evidence for the oxidation of Au^{I} to Au^{III} was not provided. Tse and co-workers themselves suggested a Friedel–Crafts-type reaction involving aryl carbocations or the participation of a coordinated cationic radical as an alternative.

Shortly afterwards, our research group reported a gold-catalyzed domino cyclization–oxidative-coupling reaction of aryl alkynoates to form dicoumarins (Scheme 8).[18] This reaction constitutes the first example of an oxidative C–C bond-forming reaction induced by the π Lewis acidity of a catalytic amount of gold. More specifically, the generation of the Au–R species relies on the π Lewis acidity of the gold catalyst; the resulting 2-Au-substituted coumarin intermediate **22** can promote a second cyclization of the starting ester **19** to generate an R–Au–R species **23**, which finally undergoes reductive elimination to form the observed dicoumarins. An alternative mechanism would be the creation of the R–Au–R intermediate **23** by transmetalation. However, a C–H insertion mechanism could be ruled out, as the monocoumarin **21** was not converted into the dimer under the reaction conditions. We used *tert*-butylhydroperoxide to regenerate the Au^{III} species. However, it is not clear which intermediate undergoes oxidation. The most obvious possibility would be the oxidation of AuCl after the reductive elimination.



Scheme 8. Synthesis of dicoumarins by a gold-catalyzed domino cyclization–oxidative-coupling reaction.

Recently, we could extend this catalytic mode of action to the domino cyclization–oxidative coupling of 2-alkynyl phenols **24** to form 3,3′-bis(arylbenzofurans) **25** (Scheme 9),[19] which turned out to be interesting photochemical substrates.[20] If a simple oxidation of $Au^{I}Cl$ occurred in the catalyst-reoxidation step, the oxidant (*t*BuOOH) used in the conversion of esters **19** into dicoumarins should also be applicable to this transformation. However, with *t*BuOOH as the oxidant, only the monobenzofuran was formed. In the reaction with PIDA as the oxidant in diethyl ether, there was a fine line between the desired reoxidation of the catalyst and decomposition of the starting material. This observation hints at a more complex oxidation step, with the substrate involved in the oxidation of the gold catalyst.

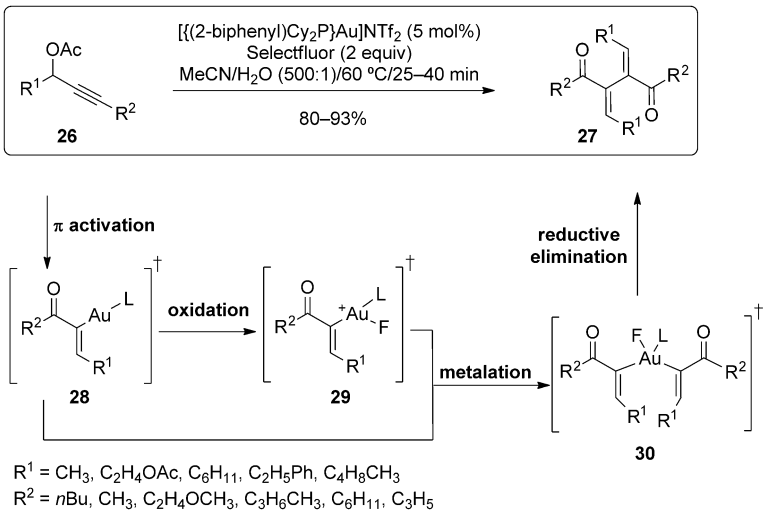


Scheme 9. Synthesis of bis(arylbenzofurans) by a gold-catalyzed domino cyclization–oxidative coupling reaction.

A similar reactivity pattern was witnessed for gold catalysts by Zhang and co-workers: when propargyl acetates **26** were treated with $[(PPh_3)Au]NTf_2$ (5 mol%) and Selectfluor in acetone at 80 °C, the formation of enone dimers (19%) was observed, with no formation of the desired α-fluoroenones.[21] This gold-catalyzed dimerization of propargylic acetates was then optimized. Different enone dimers **27** were obtained in good to excellent yields when $[\{(2\text{-biphenyl})Cy_2P\}Au]NTf_2$ (5 mol%) was used in the presence of Selectfluor (2 equiv) in a MeCN/H_2O mixture at 60 °C (Scheme 10). This study was the first to show that Selectfluor is able to oxidize an Au^{I} complex to an Au^{III} complex. In this specific example, the oxidation process is most likely facilitated by the formally negatively charged 1-acylalkenyl ligand; an oxidation of the initial catalyst $[\{(2\text{-biphenyl})Cy_2P\}Au]NTf_2$ seems less probable according to our experience described above. Detailed studies by Toste and co-workers on the role of Selectfluor are discussed together with their efforts towards the development of gold-catalyzed cross-coupling reactions in Section 4.3.[22]

4. Cross-Coupling Reactions

As Au^{I} has the same d^{10} configuration as Pd^{0} and Cu^{I}, it is thought to catalyze reactions typically promoted by Pd, that is, cross-coupling reactions. Therefore, gold catalysts were exam-

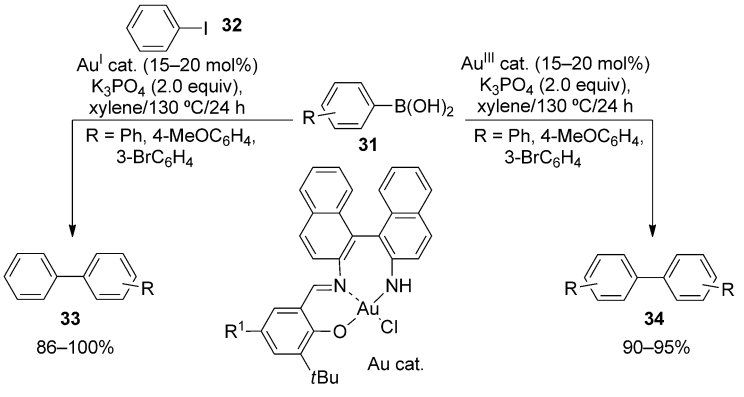


Scheme 10. Gold-catalyzed oxidative coupling of enones with Selectfluor as the oxidant. Cy = cyclohexyl, Tf = trifluoromethanesulfonyl.

ined in such "classical" cross-coupling reactions.[23] Following these developments, gold catalysis was combined in a synergistic way with palladium catalysis. Finally, research has pushed forward successfully to enable cross-coupling reactions with only gold catalysts.

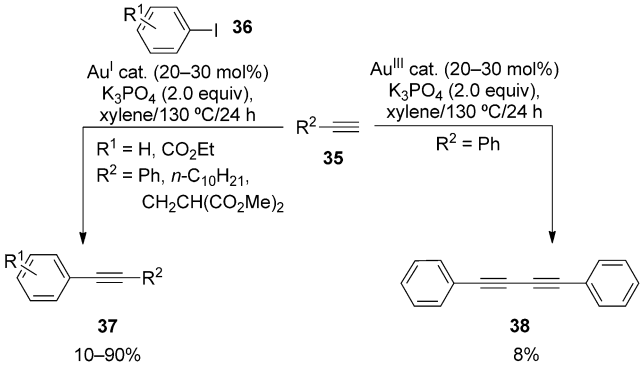
4.1. Gold Catalysts in Classical Cross-Coupling Reactions

Corma and co-workers took on the challenge to promote gold catalysts as efficient alternatives to palladium or nickel catalysts. On the basis of their initial results on the gold(III)-catalyzed homocoupling of aryl boronic acids, they investigated the potential of gold complexes for Suzuki coupling reactions.[24a] Unsymmetrical N-heterocyclic carbene–gold(I) complexes and their equivalents immobilized on silica gel, ordered mesoporous silica (MCM-41), and delaminated zeolite (ITQ-2) were successfully employed for the Suzuki coupling of PhI (**32**) with aryl boronic acids **31** in high yields and with high selectivity (Scheme 11). Higher activities were observed for supported catalysts (except for those supported on silica gel) than for nonsupported complexes.[24b] Investigations on the MCM-41 support were carried out with chiral Schiff base–gold complexes and confirmed the previously observed dichotomy: Au^{I} complexes catalyzed the cross-coupling reaction, whereas the respective Au^{III} complexes catalyzed the homocoupling of aryl boronic acids **31** to afford symmetrical biaryl compounds **34** (Scheme 11).[25]



Scheme 11. Dichotomy of Au^{I} and Au^{III} catalysis for the Suzuki or homocoupling of boronic acids.

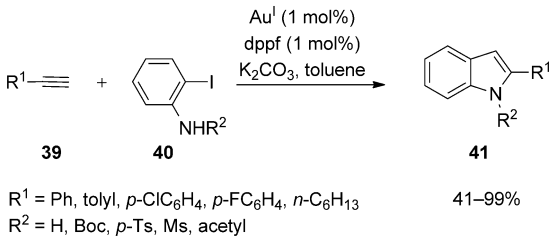
Along the same line, Corma and co-workers investigated the potential of their catalysts for the Sonogashira reaction (Scheme 12). Commercially available [AuCl(PPh_3)] and various Au^{I} and Au^{III} complexes with Schiff base ligands derived from 1,1′-binaphthyl-2,2′-diamine were studied for the Sonogashira cross-coupling of $R^1C_6H_4I$ **36** with a series of alkynes **35** containing electron-donating or electron-withdrawing substituents.[26] The results were in line with the observations for Suzuki coupling reactions: Au^{I} tended to be active and very selective for the cross-coupling reaction, whereas Au^{III} catalyzed the homocoupling condensation.



Scheme 12. Sonogashira versus homocoupling depending on the oxidation state of the gold catalyst.

In parallel, You and co-workers reported gold(I) iodide catalyzed Sonogashira reactions of terminal alkynes with aryl iodides and bromides to give the corresponding cross-coupling products in good to excellent yields in the presence of AuI and dppf (1 mol%) in toluene. The application of this procedure to the reaction of terminal alkynes **39** with 2-iodoanilines **40** afforded various substituted indoles **41** through a coupling–cyclization sequence (Scheme 13).[27]

However, in experiments designed to explain mechanistically the catalysis of cross-coupling reactions with gold, Echavarren and co-workers recently discovered that the presence of palladium contamination (0.1 mol%) might explain the successful palladium-free Sonogashira coupling reactions reported by Corma and co-workers.[28] They could convincingly show that the required oxidative addition of the gold(I) catalyst, either as AuX or as alkynylated Au–C≡CR, did not occur under any of

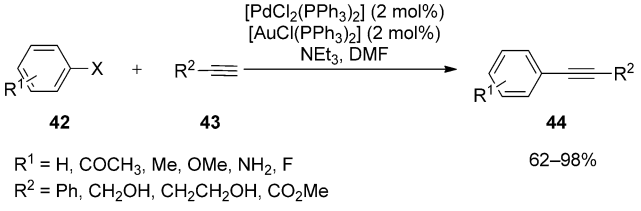


Scheme 13. Gold-catalyzed domino Sonogashira–cyclization reaction. Boc = *tert*-butoxycarbonyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, Ms = methanesulfonyl, Ts = toluenesulfonyl.

the reported conditions. However, if a source of Pd was added, the reaction partners underwent a smooth coupling reaction. Such results question the efficiency of gold alone to catalyze the cross-coupling of nonactivated arenes. It is more likely that the gold species acts in a similar way to copper salts under classical Sonogashira coupling conditions. An investigation of this discrepancy by Corma et al. led to the conclusion that Au nanoparticles that formed under the reaction conditions were responsible for the cross-coupling activity of the Au catalyst rather than distinct homogenous catalytic Au complexes.[29]

There is an ongoing interest in methods of C–C bond formation that take advantage of the synergy between gold and palladium catalysts. The orthogonal reactivity of the two metals is thought to be a guarantee for highly selective reactions. Laguna and co-workers[30] as well as Panda and Sarkar reported the activity of the dual catalytic system [$PdCl_2(PPh_3)_2$]/[$AuCl(PPh_3)$] (each 2 mol%) for the Sonogashira reaction of alkynes with aryl halides in good to excellent yields (62–98%; Scheme 14).[31]

By using another catalytic duo, $PdCl_2$/AuCl, Panda and Sarkar were able to efficiently synthesize nonsymmetrical biaryl acetylenes by Sonogashira-type cross-coupling reactions of arene diazonium salts prepared in situ from anilines and terminal alkynes.[32] No trace of a Hay–Glaser-type homocoupling of alkynes was observed in any of the reactions. The authors did not investigate the mechanism but assumed gold acetylides to be intermediates which enter into the Pd catalytic cycle as proposed by Echavarren and co-workers.

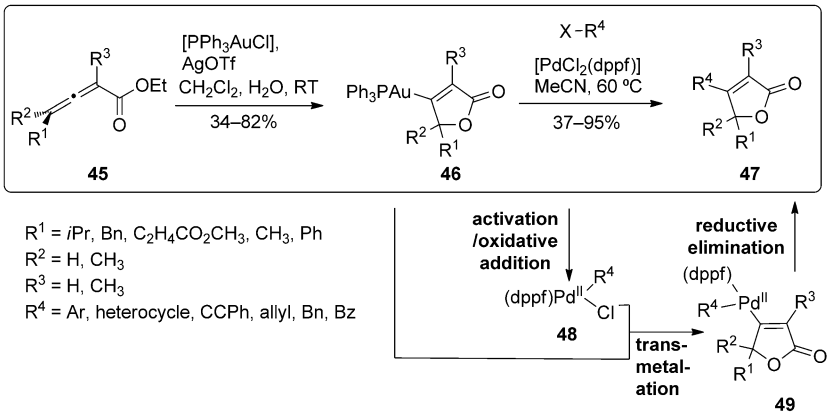


Scheme 14. Palladium/gold-cocatalyzed Sonogashira reaction described by Panda and Sarkar. DMF = *N*,*N*-dimethylformamide.

4.2. Gold Species in Palladium-Catalyzed Coupling Reactions

In 2009, Hashmi et al. developed another option to broaden the scope of homogeneous gold catalysis: the transmetalation of organogold species generated in situ to another transition metal, such as a palladium catalyst.[33] In this approach, strong oxidants can be avoided, which leads to higher functional-group tolerance.

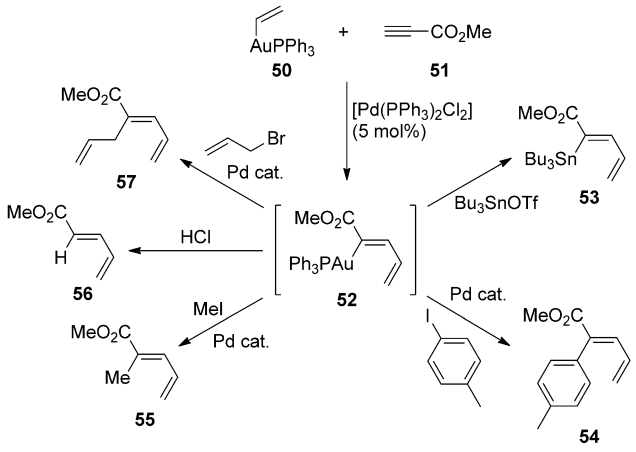
Organogold(I) compounds were synthesized by transmetalation reactions from electropositive metals, such as lithium, magnesium, or boron. Hashmi et al. also used a stable vinyl gold intermediate obtained by the gold-catalyzed allene cycloisomerization reaction developed by Hammond and co-workers.[34] The corresponding cross-coupling products were obtained by treatment of the organogold compounds with aryl iodides in the presence of [$PdCl_2$(dppf)] (1 mol%) in acetonitrile (Scheme 15).[33] The reactions were carried out



Scheme 15. Combination of gold and palladium for cross-coupling. Bz = benzoyl.

under very mild conditions, and the solvent had no significant influence; no additives were necessary. Vinyl gold species **46** obtained by gold-catalyzed allene cycloisomerization were shown to be efficient substrates for palladium-catalyzed cross-coupling reactions with a variety of electrophiles (aryl halides, heterocyclic halides, alkynyl halides, allylic substrates, benzyl bromide, and acid chlorides). The functional-group tolerance turned out to be very high, and complete conversion was observed within 4 h.[35] Again, these results support the mechanistic studies by Echavarren and co-workers.

Blum and co-workers reported a similar transformation involving the palladium-catalyzed *syn* carboauration of alkynes with organogold reagents.[36] The reaction proceeded with complete regioselectivity at room temperature and led to the formation of α-methoxycarbonyl substituted vinyl gold intermediate **52** within a few hours (Scheme 16). The observed *syn* selectivity is opposite to that observed in the examples reported by Toste and co-workers for the intramolecular carboauration of alkynes without a Pd catalyst.[37] Notably, the stability to protodeauration of these vinyl gold intermediates enables their isolation by chromatography on silica gel or alumina and their successful use in one-pot

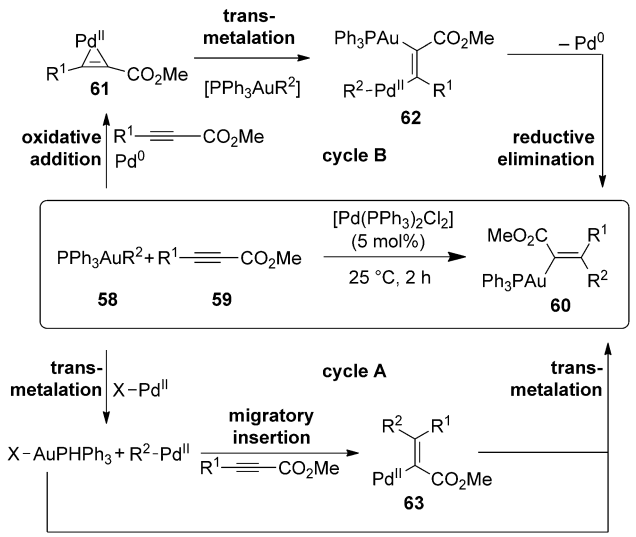


Scheme 16. Palladium-catalyzed carboauration of an alkyne and palladium/gold-catalyzed cross-coupling reactions.

palladium-catalyzed carboauration/functionalization sequences with retention of configuration (Scheme 16).

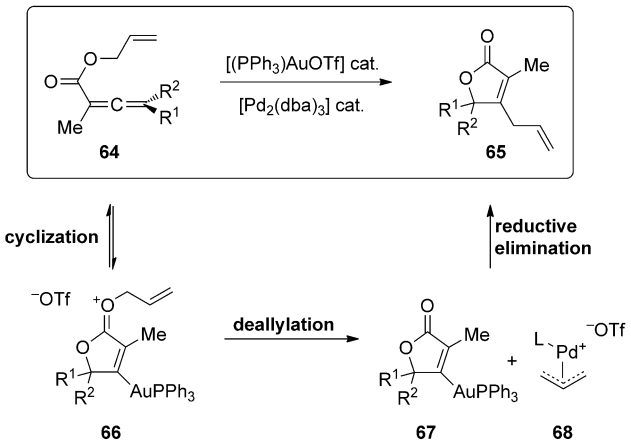
Blum and co-workers proposed two catalytic cycles for this palladium-catalyzed carboauration (Scheme 17). In cycle A, the gold reagent is involved in two transmetalation steps, and the oxidation state of the palladium catalyst remains constant during the reaction; in cycle B, oxidative addition is followed by transmetalation and reductive elimination in a Pd^0/Pd^{II} cycle similar to that of well-known palladium-catalyzed cross-coupling reactions. Investigations of analogous reactions confirmed the viability of a vinyl transmetalation reaction between Pd and Au. However, the authors could not decide in favor of one of the two possible catalytic cycles.

One major drawback of the procedures developed by the research groups of Hashmi and Blum is the use of a stoichiometric amount of gold to synthesize the vinyl gold intermediates. Subsequently, Blum and co-workers reported



Scheme 17. Mechanistic alternatives proposed for the palladium-catalyzed carboauration of alkynes.

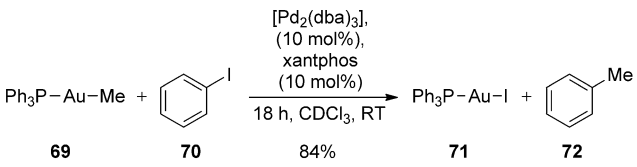
the new concept of "catalyzed catalysis".[38] They used a carbophilic Lewis acidic Au catalyst to promote the cross-coupling reactivity of a Lewis basic Pd catalyst in order to functionalize vinyl gold intermediates formed by intramolecular substrate rearrangements (Scheme 18). Gold catalyzes



Scheme 18. Proposed mechanism for the gold/palladium-catalyzed rearrangement to form butenolides.

both the initial rearrangement step and the subsequent oxidative addition of palladium, first by lowering the energy of the allene antibonding orbital and then by redistributing this electron deficiency through the substrate rearrangement by lowering the energy of the allyl–oxygen antibonding orbital in the oxonium ion and thus lowering the barrier for oxidative addition by the Pd catalyst. The allyl oxonium ion **66** generated by Au^I catalysis undergoes deallylation, which leads to a neutral vinyl gold compound **67** and a π-allyl Pd^{II} complex **68**. The formation of the C–C bond by reductive elimination regenerates the Au and Pd catalysts, which can reenter the catalytic cycle. Interestingly, this principle is showcased in a very similar reaction reported by Hashmi et al.,[33] who had to use a stoichiometric amount of gold. The key to the use of gold as a catalyst seems to be the generation of the Pd–R species (in this case palladium–allyl) without the generation of halogen ions, which inhibit catalytic turnover owing to their high affinity for gold.

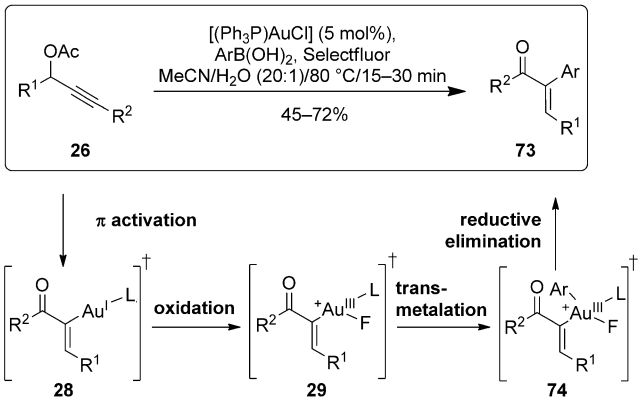
A first encouraging result was recently presented for the notoriously difficult cross-coupling of alkyl–metal species (in this case [(Ph_3P)AuMe] (**69**)) with aryl halides under the catalysis of Pd.[39] The transformation has not yet been shown to be of broad generality, as only the example shown with iodobenzene (**70**) was reported (Scheme 19).



Scheme 19. Palladium-catalyzed cross-coupling of an alkyl–gold reagent. dba = dibenzylideneacetone.

4.3. Gold-Catalyzed Cross-Coupling Reactions

Building on their experience with the gold-catalyzed dimerization of propargylic acetates in the presence of Selectfluor, Zhang and co-workers bridged the gap to the obvious next level by using boronic acids as coupling partners with a gold intermediate **28** generated from a propargylic acetate and a π Lewis acidic gold catalyst (Scheme 20).[40] The



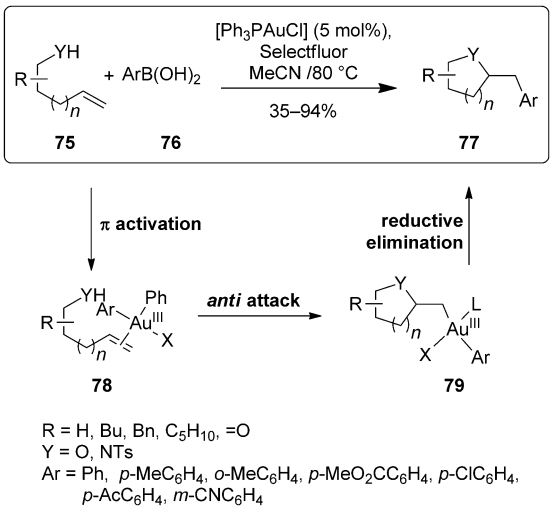
R^1 = H, Me, *i*Pr, Ph, C_2H_4OAc, C_6H_{11}, C_2H_5Ph, *p*-BrC_6H_4
R^2 = *n*Bu, $C_2H_4OCH_3$, C_6H_{11}, Ph
Ar = Ph, *p*-MeC_6H_4, *p*-$MeO_2CC_6H_4$, *p*-ClC_6H_4, *m*-$MeO_2CC_6H_4$

Scheme 20. Gold-catalyzed cross-coupling reaction of alkynyl acetates with aryl boronic acids.

process showed excellent *E* selectivity: no *Z* isomers were detected. In the mechanism proposed by Zhang and co-workers for this transformation, Selectfluor oxidizes the vinyl gold(I) intermediate **28** generated by coordination of Au to the alkyne and subsequent hydrolysis. The Au^{III} species **29** formed can then undergo transmetalation with an external organometallic reagent, in this case a boronic acid, and release an enone **73** upon reductive elimination.

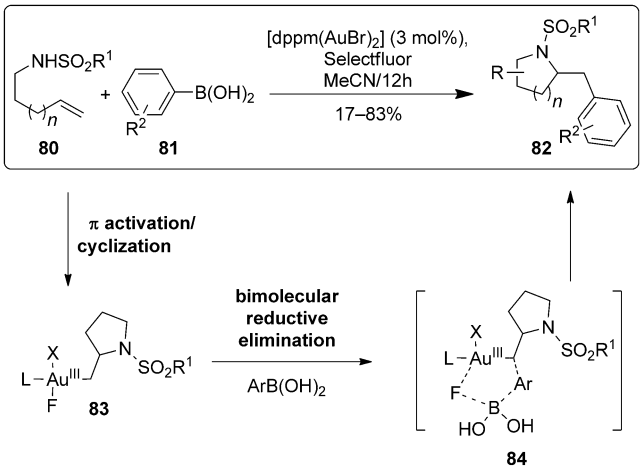
However, in their most recent report on the gold-catalyzed carboheterofunctionalization of alkenes, the same research group proposed a slightly different mechanism involving the initial oxidation of Au^I to Au^{III} by Selectfluor.[41] They described the first example of the catalytic conversion of a C_{sp^3}–Au bond into a C_{sp^3}–C_{sp^2} bond through an intermolecular oxidative cross-coupling. The results of deuterium-labeling studies support the *anti* nature of the auroheterofunctionalization of the alkenes and the existence of Au^I/Au^{III} catalysis (Scheme 21).

Toste and co-workers reported a very similar transformation.[42] Detailed mechanistic studies revealed that the reductive elimination proceeds via a bimolecular transition state **84** involving an intermediate $RAu^{III}FX$ as well as the boronic acid (Scheme 22). The reaction tolerated a wide variety of sulfonamides and boronic acids, both electron-rich and electron-poor. On the basis of the same mechanistic rationale, Toste and co-workers developed a three-component coupling for the oxidative oxyarylation of alkenes.[43] Shortly after that, Mankad and Toste isolated and characterized an $Au^{III}F$ complex that supports the initial proposal.[44] The catalytic



R = H, Bu, Bn, C_5H_{10}, =O
Y = O, NTs
Ar = Ph, *p*-MeC_6H_4, *o*-MeC_6H_4, *p*-$MeO_2CC_6H_4$, *p*-ClC_6H_4, *p*-AcC_6H_4, *m*-CNC_6H_4

Scheme 21. Gold-catalyzed carboheterofunctionalization of alkenes.



R^1 = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *p*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$
R^2 = H, 3-F, 2-Cl, 4-CO_2Me, 2-CO_2Me, 4-CHO, 4-Me, 4-MeO

Scheme 22. Mechanistic proposal for the role of Selectfluor in the gold-catalyzed coupling reaction with boronic acids.

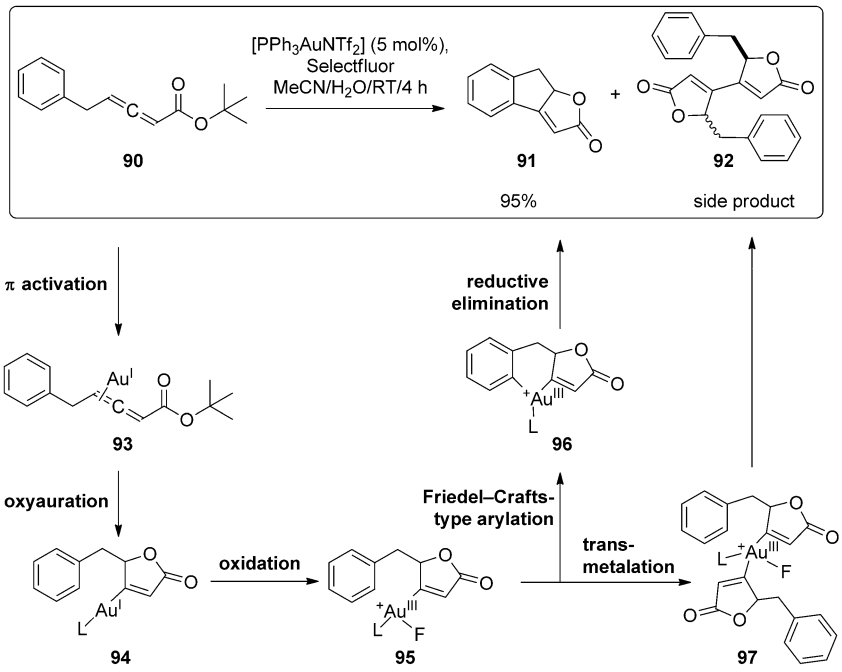
principle was extended by the same research group from boronic esters to aryl trimethylsilanes[45] in a reaction that was disclosed simultaneously by Lloyd-Jones and co-workers.[46]

De Haro and Nevado integrated the 5-*exo* cyclization of alkenyl amines with an intramolecular C–H functionalization in an elegant approach to 3-benzazepines. A hypervalent iodine reagent was used to reoxidize the Au catalyst (Scheme 23).[47]

While investigating gold-catalyzed fluorination methods with Selectfluor as a powerful electrophilic fluorine source,[48] Gouverneur and co-workers quickly realized the potential of the oxidation properties of such electrophilic N–F reagents in connection to Au catalysis. In 2010, the group reported the first gold-catalyzed oxidative cross-coupling reaction by intramolecular C–H arylation (Scheme 24).[49] Besides the tricyclic cross-coupling product **91**, the formation of a mixture

of dimeric butenolides **92** resulting from intermolecular homocoupling was also observed. The proposed mechanism involves the initial coordination of Au^{I} to the allene and addition of the pendent *tert*-butyl ester to afford intermediate **94**. Then, oxidative fluorination to give the Au^{III} species **95** is followed by Friedel–Crafts-type arylation with fluoride displacement to form the auracycle **96**, an intermediate susceptible to Au^{III}/Au^{I} reductive elimination, which releases the tricyclic product **91**.

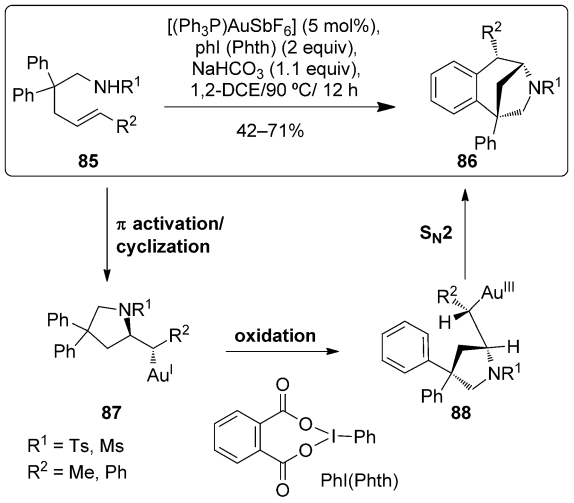
Recently, the same research group reported a variation on the gold-catalyzed oxidative intramolecular C–H arylation of allenoate esters: the gold(I)-catalyzed cascade cyclization–oxidative alkynylation of allenoate **98** to give β-alkynyl γ-butenolide **100** (Scheme 25).[50] Following an initial gold-catalyzed C–O bond-forming allenoate cyclization, an oxidative cross-alkynylation occurs. Two possible mechanistic pathways were proposed for the formation of β-alkynyl γ-butenolide **100**, both of which involve an Au^{I}/Au^{III} redox cycle; one commences with the π activation of the allene **98**, and the other starts with the metalation of the alkyne **99**. Both pathways converge at an Au^{III} intermediate **105**, which collapses by reductive elimination to the final alkynyl butenolide **100**. Investigations on the different mechanisms did not enable discrimination between the two pathways.



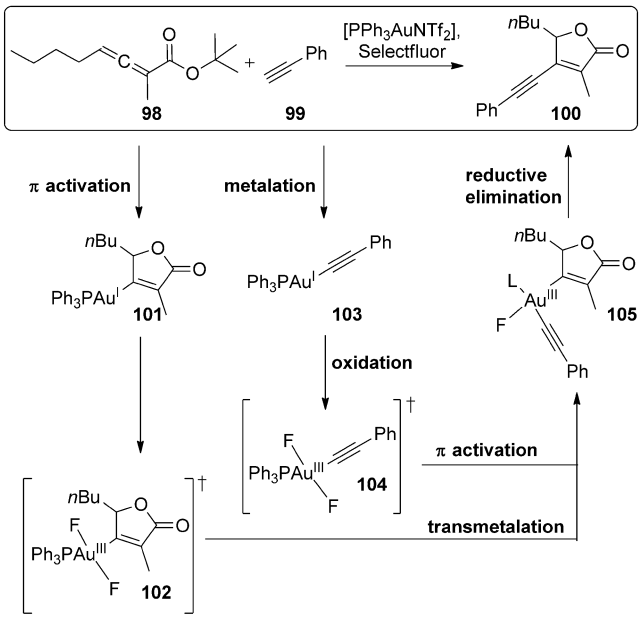
Scheme 24. Cyclization and intramolecular cross-coupling reaction to form a tricyclic butenolide.

Waser and co-workers followed a different strategy for the cross-coupling of pyrroles and indoles,[51] as well as thiophene heterocycles,[52] with alkynyl iodonium salts **107** (Scheme 26). In this case, the oxidant is incorporated in the coupling reagent. Two different mechanistic pathways were hypothesized: π activation of the alkynyl iodonium salt **107**, followed by a Friedel–Crafts-type arylation and subsequent elimination, or oxidation of the gold catalyst, which metalates the heterocycle and forms the product **108** through reductive elimination.

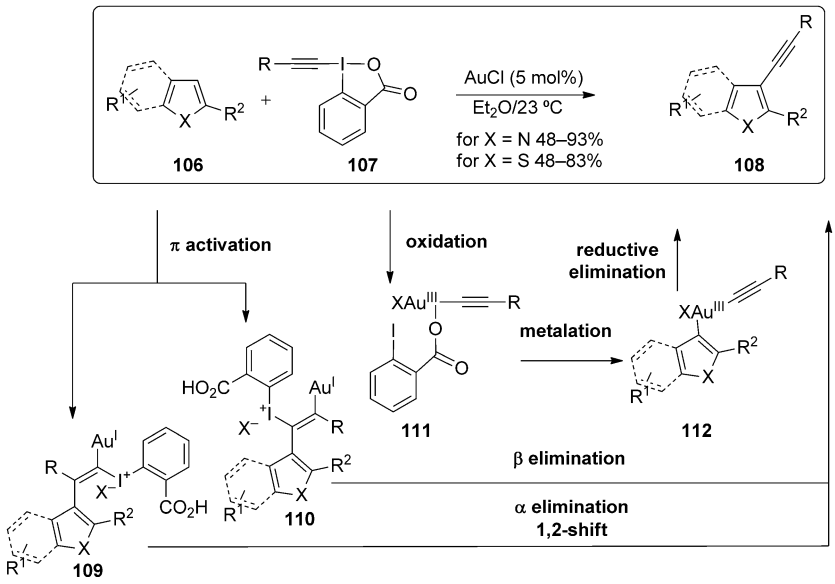
A similar reaction for the alkynylation of Ar–H bonds was presented by de Haro and Nevado.[53] They also relied on



Scheme 23. Access to 3-benzazepines through a gold-catalyzed 5-*exo* cyclization/oxidative C–H functionalization. DCE = 1,2-dichloroethane.



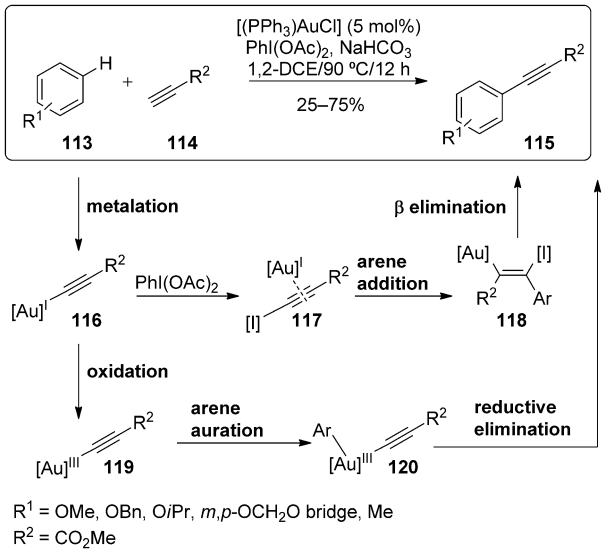
Scheme 25. Gold(I)-catalyzed cascade cyclization–oxidative alkynylation of allenoates to form β-alkynyl γ-butenolides.



X = NH, NMe, NOMe, NOH, NCN, NCO_2H, NNO_2, N-halogen, S
R^1 = heterocycle
R^2 = H, CH_3, CH_2OH, Ph
R = $SiMe_3$, Si*i*Pr

Scheme 26. Alkynylation of indoles, pyrroles, and thiophenes.

a hypervalent iodine species as the oxidant of the gold catalyst, but in this case an external reagent, $PhI(OAc)_2$ (Scheme 27). Again, two mechanistic pathways were suggested: The first step is in both cases the metalation of the terminal triple bond; the resulting intermediate **116** was isolated and characterized. Subsequently, insertion into the Ar–H bond can occur to give **120**, followed by reductive elimination to give the desired product. The alternative involves the conversion of the gold–acetylene complex into the hypervalent iodine reagent, which is then activated by



R^1 = OMe, OBn, O*i*Pr, *m*,*p*-OCH_2O bridge, Me
R^2 = CO_2Me

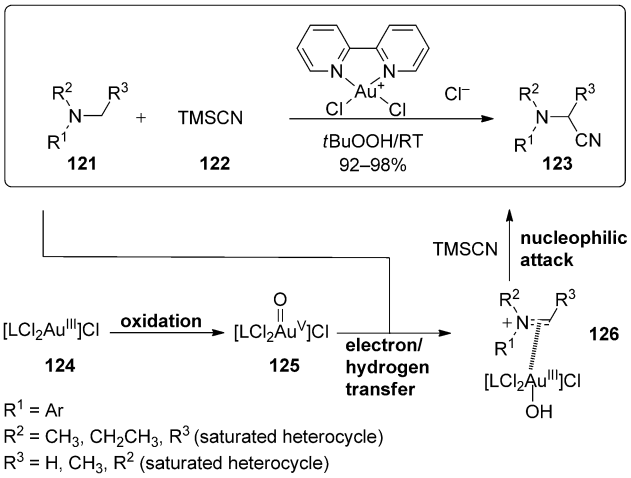
Scheme 27. Gold-catalyzed oxidative cross-coupling of alkynes with Ar–H bonds.

gold as a π Lewis acid. A Friedel–Crafts-type arylation then occurs, followed by elimination to generate the triple bond.

Very recently, Zhu and co-workers reported an oxidative α cyanation of tertiary amines with a 2,2′-bipyridine–gold complex (Scheme 28).[54] This complex was proposed to be oxidized by *t*BuOOH to an Au^V species **125**, which then transforms the starting amine into an ammonium-ion intermediate **126** by electron and subsequent hydrogen transfer. However, as the only known Au^V species are gold fluorides such a mechanistic option is unlikely.

5. Conclusion and Outlook

In the past few years, the use of gold catalysts for C–C coupling reactions has been demonstrated and taken beyond the simple replacement of "classic" coupling catalysts, such as Pd and Ni. The combination of the oxidation/reduction chemis-



R^1 = Ar
R^2 = CH_3, CH_2CH_3, R^3 (saturated heterocycle)
R^3 = H, CH_3, R^2 (saturated heterocycle)

Scheme 28. α Cyanation of tertiary amines. TMS = trimethylsilyl.

try of gold with its unique ability to act as a mild π Lewis acid promises enormous potential. However, although mechanistic understanding of the π Lewis acid character of gold has progressed tremendously, investigations into the fundamental oxidative-addition, transmetalation, and reductive-elimination steps of C–C bond formation with gold catalysts, and above all the oxidation/reduction chemistry of gold catalysts in organic transformations, are still in their infancy. This aspect is not only represented by the standard closing sentence of most of the publications presented in this Minireview, that "The exact mechanism for product formation is not clear …", but also by a constant change in

mechanistic proposals, which is the fundamental principle of the development of scientific knowledge. Therefore, a lot of research in this promising area of catalysis is waiting to be done before gold catalysts will truly get their place as versatile tools for C–C coupling reactions.

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