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Fundamental Basis for Implementing Oxidant-Free Au(I)/Au(III) Catalysis

Pau Font[a] and Xavi Ribas*[a]

Oxidant-free Au(I)/Au(III) catalysis can still be regarded as a young and promising chemistry. Because the first examples of gold catalysis were limited to the activation and functionalization of π-C—C bonds and very little was known on fundamental organometallic transformations at gold, countless works during the past 15 years have been devoted to disclosing the elementary reactivity of gold and implementing it in catalysis. Remarkably, great emphasis on triggering oxidative addition at Au(I) has been placed, as the high redox potential of the Au(I)/Au(III) pair disfavors this reaction. In fact, different strategies such as strain release, ligand design and photochemistry have been proven successful at allowing the bottleneck oxidative addition to occur. These approaches have led to the rational development of oxidant-free Au(I)/Au(III) redox catalysis, particularly catalytic cycles in cross-coupling transformations where oxidative addition is usually the entry point to the cycle. Herein, the background story, the development process, and relevant examples of oxidant-free gold-catalyzed cross-coupling reactions are reviewed.

1. The Early Years of Homogeneous Gold Catalysis

The field of homogeneous gold chemistry has experienced a large development the past 25 years, from the late 90's until present. Gold had previously been regarded as a chemically inert metal due to its remarkable air and moisture stability and because scarce examples of gold-mediated transformations were known by that time.[1] Thus, the disclosure by the end of the 20th century of the so-called π-activation chemistry, in which gold complexes reacted as carbophilic Lewis acids capable of activating π-C—C bonds of alkenes, alkynes and allenes toward nucleophilic attacks, was a breakthrough in gold chemistry (Figure 1).[2] Since then, huge research efforts were devoted to exploit this chemistry, emerging as a very useful method for organic synthesis, as new C—heteroatom and C—C bond couplings could be selectively formed by means of homogeneous catalysis under mild conditions.
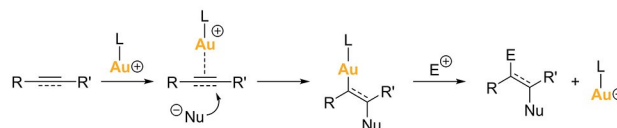
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Figure 1. General scheme of gold-catalyzed π-activation and functionalization of multiple C—C bonds.

1.1. Redox-Neutral Gold Catalysis: π-Activation of C—C Multiple Bonds

In π-activation, the oxidation state of the gold center does not change throughout the process, fact that stands in stark contrast to well-known cross-couplings catalyzed by other late transition metals. Typically, Au(I) complexes or Au(III) salts are employed as catalysts. Among the wide literature on gold-mediated activation and functionalization of C—C multiple π-bonds, some works can be highlighted as examples to illustrate the vast variety of transformations that can be achieved.[2–3] In this line, additions of O- and N-nucleophiles to alkynes,[4] hydroamination of alkynes, allenes and alkenes (Figure 2a),[5] cyclization of allenyl ketones, α,β-unsaturated ketones and alcohols,[6] intermolecular addition of phenols and carboxylates to terminal alkenes (Figure 2b),[7] and intramolecular rearrangements (Figure 2c),[8] among other transformations, were demonstrated to afford the corresponding products through the above-described general gold-catalyzed π-activation mechanism.

1.2. Au(I)/Au(III)-Catalyzed Oxidative Couplings

Transition-metal-catalyzed cross-coupling transformations are usually based on catalytic cycles that comprise the interconver-

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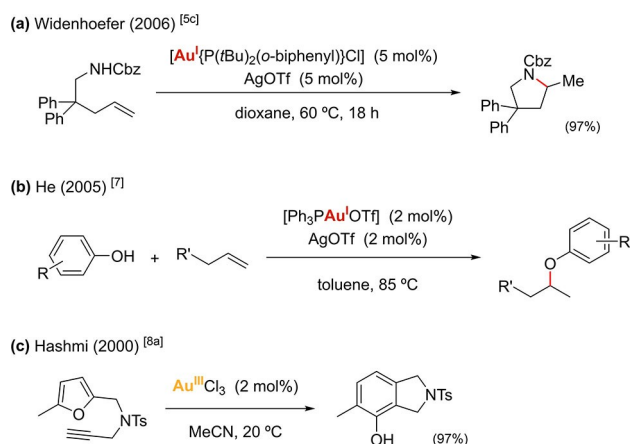Europe**
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Figure 2. (a) Gold-catalyzed intramolecular hydroamination of a terminal olefin. (b) Gold-catalyzed intermolecular addition of phenols to olefins. (c) Gold-catalyzed intramolecular cycloisomerization of a furan with a terminal alkyne moiety.

Figure 3. Mechanistic proposal for Au(I)/Au(III)-catalyzed oxidative cross-coupling reactions.

sion between different oxidation states of the metallic atom which is generally achieved via two-electron redox steps, namely oxidative addition and reductive elimination.[9] Palladium has typically been the metal of choice for catalyzing a vast array of cross-coupling transformations, therefore countless Pd(0)/Pd(II)[10] and Pd(II)/Pd(IV)[11] catalytic cycles have been reported to be the operating mechanisms in Pd-mediated couplings. Nevertheless, many other transition metals have also shown to be good candidates as catalysts in cross-coupling transformations. Thus, examples of Ni(0)/Ni(II)-,[12] Ni(I)/Ni(III)-,[13] Ni(II)/Ni(IV)-,[14] Co(I)/Co(III)-[15] Cu(I)/Cu(III)-[16] and Au(I)/Au(III)-catalyzed cross-couplings can be found out there in the literature, among others. The case of gold, however, can be regarded as special since, due to its strong relativistic effects,[17] the Au(I)/Au(III) pair features an unusual high redox potential ($E^0 = 1.41$ V vs. SHE in water) compared to that of the isoelectronic Pd(0)/Pd(II) pair ($E^0 = 0.92$ V).[18] This peculiarity is precisely what makes Au(I) especially reluctant to oxidative addition[19] so, in order to build Au(I)/Au(III) catalytic cycles, stoichiometric amounts of external oxidants have traditionally been employed to promote, via a 2-electron oxidation instead of oxidative addition, the formation of the envisioned key Au(III) intermediates (Figure 3Typical sacrificial oxidants are F^+ donors, such as Selectfluor or N-Fluorobenzenesulfonimide (NFSI), and hypervalent iodine reagents. Following this strategy, a wide
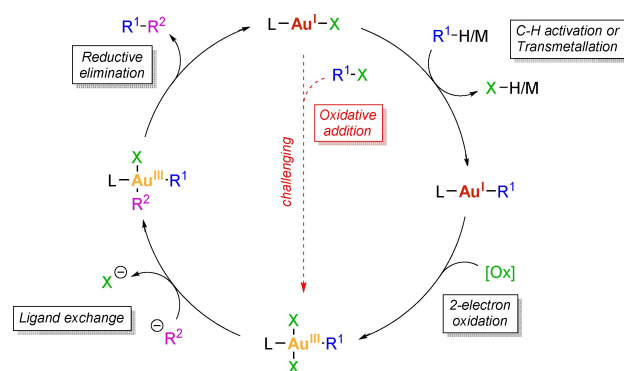
assortment of Au(I)/Au(III)-catalyzed oxidative couplings exists,[3b,20] including C—C and C—X couplings at alkenes, allenes, alkynes and arenes. In 2008, Tse and coworkers published the first gold-catalyzed C—C coupling to yield biaryls, using 2 mol% $HAuCl_4$ and $PhI(OAc)_2$ as a sacrificial oxidant.[21] In 2009, Zhang and coworkers used propargylic acetates to develop the corresponding Au(I)/Au(III)-catalyzed oxidative dimerization as well as the oxidative coupling with arylboronic acids.[22] In both transformations, the Au(III) intermediate species were proposed to be formed from the Selectfluor-promoted oxidation of the corresponding Au(I) species.

From 2010 to 2012, several research groups reported independently numerous studies on gold-catalyzed oxy- and aminoarylation reactions at olefins (Figure 4). Russell and Lloyd-Jones employed arylsilanes as coupling fragments in two- and three-component gold-catalyzed oxyarylation of terminal alkenes.[23] In this work, the use of Selectfluor not only allowed the access to a Au(I)/Au(III) catalytic cycle but also avoided the need for adding a stoichiometric base as it provided a fluoride anion for silane activation. In the same line, two years later, the same group expanded the scope of compatible olefins to styrenes and mono- and gem-disubstituted olefins in Au-catalyzed three-component oxyarylations by employing iodoso-benzoic acid (IBA) as oxidant instead of Selectfluor.[24] In parallel, the group of Toste also studied the three-component gold-catalyzed oxyarylation of terminal olefins employing the bimetallic gold(I) complex [dppm(AuBr)$_2$][25] and could expand the scope of the arylating fragment from arylsilanes to arylboronic acids (Figure 4a).[26] In addition, they developed the

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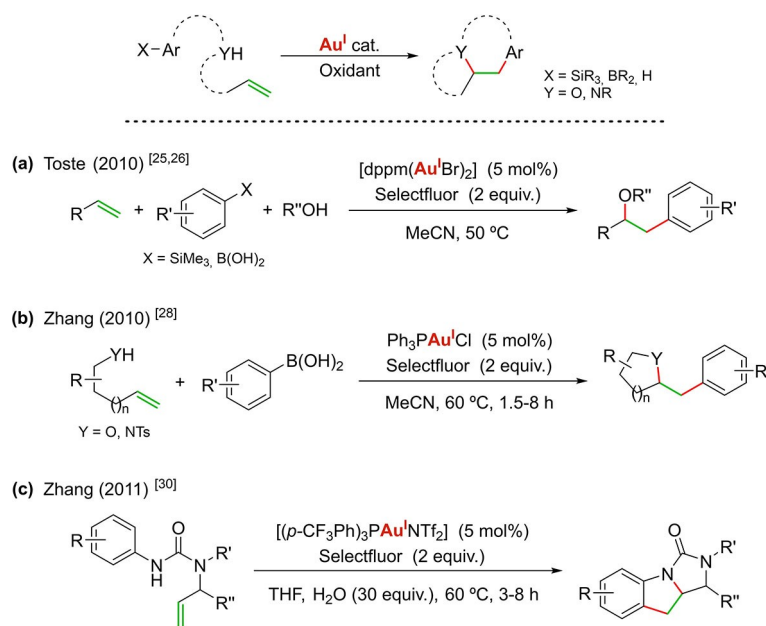
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Figure 4. General Au(I)/Au(III)-catalyzed oxy- and aminoarylations of terminal alkenes. (a) Three-component oxyarylation of terminal olefins using arylsilanes and boronic acids as competent arylating agents. (b) Two-component oxyarylations and aminoarylations of terminal alkenes using arylboronic acids. (c) Aminoarylation of terminal alkenes via intramolecular C—C coupling.

intramolecular aminoarylation of terminal alkenes using the same [dppm(AuBr)$_2$] complex, arylboronic acids as coupling partners and Selectfluor as oxidant.[27] Simultaneously, Zhang and coworkers also worked in the use of arylboronic acids for both the oxyarylation and aminoarylation of olefins, employing Ph$_3$PAuCl and Selectfluor (Figure 4b).[28] In addition, Gouverneur and coworkers reported the intramolecular oxidative C—C cross-coupling of non-activated arenes to yield tricyclic dihydroindenofuranone-type products.[29] Similarly, in 2011 the group of Zhang combined the oxidative Au(I)/Au(III)-catalysis with C—H functionalization to yield tricyclic indolines as formal intramolecular [3 + 2] annulation products (Figure 4c).[30] Nevado and de Haro reported in 2010 the gold-mediated oxidative C(sp)–C(sp2) coupling of arenes with electron-deprived terminal alkynes to yield arylacetylenes (Figure 5a).[31] This work stands as the first ethynylation reaction of this kind occurring via a gold-catalyzed C—H activation of both aromatic and acetylenic counterparts. Additionally, the group of Zhang published an unprecedented gold-catalyzed Sonogashira cross-coupling of terminal alkynes with arylboronic acids.[32] The group of Shi reported the formation of unsymmetrical 1,3-diynes by reacting two different terminal alkynes under gold-catalyzed oxidative cross-coupling conditions (Figure 5b).[33] Lloyd-Jones and Russell synthesized biaryls by reacting arylsilanes with non-activated arenes, using a Au(I) catalyst and PhI(OAc)$_2$ as oxidant under mild conditions (Figure 5c).[34] In 2015, the group of Larrosa published the first gold-catalyzed oxidative cross-coupling of arenes via double C—H activation (Figure 5c).[35] The biaryls obtained consisted of the coupling between highly activated (hetero)arenes and perfluorinated arenes. This strategy, how-

ever, required the employment of silver salts to help at the C—H activation of the electron-deficient arene counterpart.

Later, Nevado and coworkers also contributed to the field of gold-catalyzed oxidative couplings to yield biaryls by providing a system in which strong electron-poor fluorinated aryl boronates coupled to arenes efficiently (Figure 5c).[36] The intermediacy of Au(III) species of the type [Au(OAc)$_2$(Ar^F)(PPh$_3$)] obtained upon PhI(OAc)$_2$-mediated oxidation could be validated. Interestingly, in 2017, Lloyd-Jones and coworkers developed an intramolecular system for the gold-catalyzed arylation of arenes by aryl-trimethylsilanes.[37] The biaryl coupling generated products featuring 5- to 9-membered rings. Tethering of the arene to the arylsilane provided the system with the ability to tolerate a wide range of electron donating and electron withdrawing arene substituents.

2. Synthesis of Well-Defined Au(III) Complexes via Oxidative Addition

In parallel with the development of gold-catalyzed oxidative cross-couplings, increasing interest arose on studying the behavior of gold complexes towards fundamental organometallic transformations and their involvement in catalytic cycles.[38] Oxidative addition is a pivotal step in organometallic chemistry as it is the entry point to most of the catalytic transformations, especially cross-coupling reactions. The ability of gold to undergo oxidative addition, in sharp contrast to other transition metals, remained elusive and scarcely investigated for a long time (see Figure 3).[18–19] However, stunning
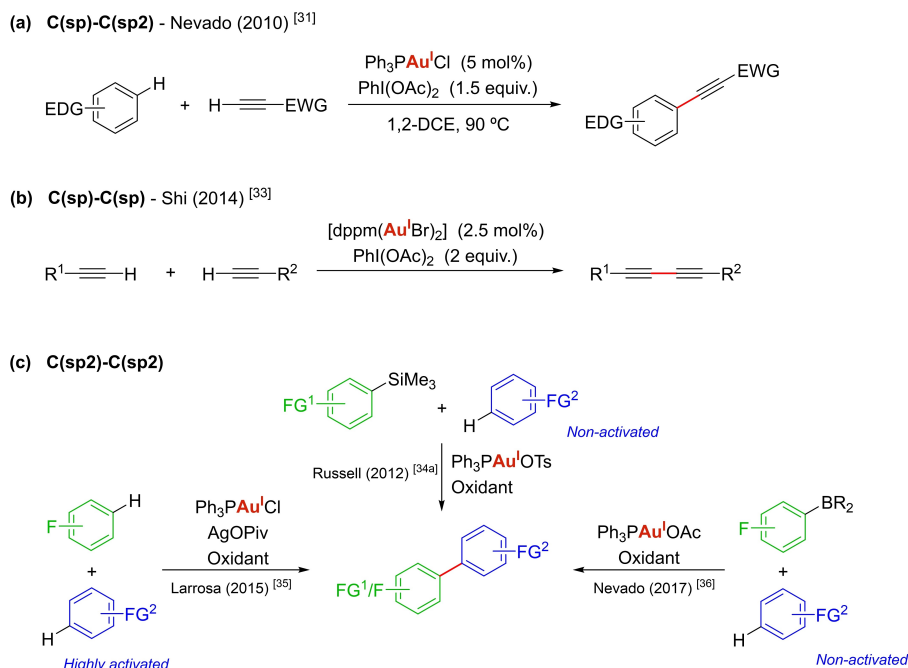
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Figure 5. (a) Au(I)/Au(III)-catalyzed ethynylation of arenes occurring via double C–H bond activation. (b) Au(I)/Au(III)-catalyzed oxidative C(sp)–C(sp) coupling for the formation of unsymmetrical 1,3-diynes. (c) Different protocols for the synthesis of biaryls by means of gold-catalyzed oxidative C(sp2)–C(sp2) cross-coupling strategies.

advances in homogeneous gold redox chemistry have been achieved over the past 7 years, demonstrating that gold is, indeed, much less inert than previously thought two decades ago. In fact, to date, many well-defined Au(III) complexes have been obtained via oxidative addition, isolated, and characterized. Strategies like strain release, ligand design and photochemistry have been proven helpful in overcoming the high redox potential of the Au(I)/Au(III) pair and trigger the otherwise sluggish oxidative addition to Au(I).

In 1967, Davison and coworkers reported the reaction between cis-bis(trifluoromethyl)-1,2-dithietene and Ph₃PAuCl to yield a chlorotriphenylphosphonium tetrathiolatoaurate salt, a Au(III) species obtained via oxidative addition of two S–S disulfide bonds to Au(I) (Figure 6a).[39] Its molecular structure was elucidated by Ibers soon after in 1968 by means of X-ray crystallography.[40] Some independent studies done by Kochi, Puddephatt and Schmidbaur in the early 1970's showed how

phosphine gold(I) methyl complexes reacted with methyl iodide to yield ethane and phosphine gold(I) iodide.[1a,b, 41] Further studies on the mechanism revealed the oxidative addition of the C(sp3)–I bond to Au(I) and in certain cases the ensuing Au(III) complexes could be characterized, depending on the phosphine donor ligand.[1c,d,42]

Despite these early studies published from 1967 to 1975, the investigations on the field of oxidative addition at gold(I) were not resumed until 2011, and experienced a dramatic growth from then on. It is worth mentioning the work published in 2008 by Gray and coworkers, where strongly activated disulfides underwent facile and reversible oxidative addition to dithiolate Au(I) complexes (Figure 6b).[43]

2.1. Strain Release to Promote Oxidative Addition at Au(I)

In 2015, Toste and coworkers reported the intermolecular oxidative addition of the strained C–C bond in biphenylene to the coordinatively unsaturated NHC–Au(I) cationic complex formed upon chloride abstraction of the (NHC)AuCl starting complex (NHC=IPr) using AgSbF₆.[44] The ensuing cationic Au(III) complex was trapped either with nBu₄NCl or with DMF to yield the corresponding tetracoordinate [(IPr)Au(III)(biphenyl)Cl] and [(IPr)Au(III)(biphenyl)(DMF)]SbF₆ complexes, which could be characterized by X-ray crystallography (Figure 7). This work outstands for being an example on how the oxidative addition of a bidentate substrate is favored because it is driven by the energy release from a strained covalent bond and because the
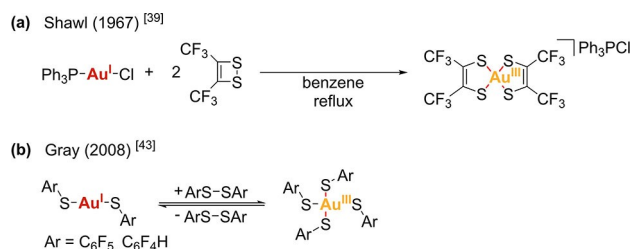

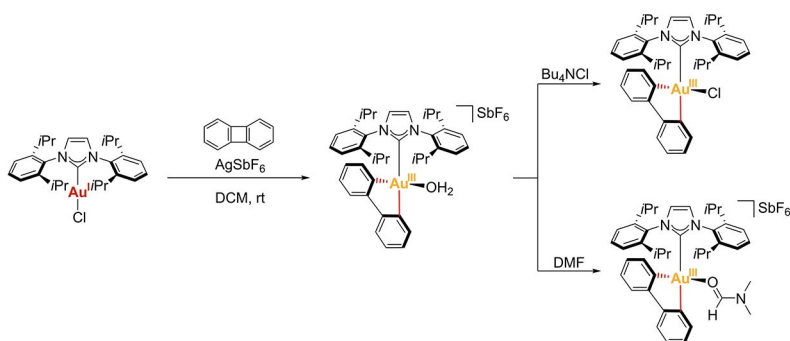**Figure 6.** Early reported examples of oxidative addition of disulfide bonds to Au(I).

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Figure 7. Oxidative addition of the strained C—C bond in biphenylene to a cationic [(NHC)Au(I)]⁺ fragment disclosed by Toste.[44a]

substrate, once coordinated, stabilizes the gold(III) center by providing it with a proper coordination geometry.

2.2. Ligand Design to Promote Oxidative Addition at Au(I)

Chelation-assisted strategy. The chelation-assisted strategy is based on generating a Au(I) complex that is coordinated to a ligand that bears a functional moiety in a right position and in close proximity to the metal center, which becomes susceptible to undergo oxidative addition to the Au(I) atom. By means of this strategy, the oxidative addition of apolar σ-bonds (E—E, where E = Si, Sn) and polarized C—X bonds to Au(I) has been achieved.

From 2011 to 2014, Amgoune, Bourissou and coworkers worked on the spontaneous intramolecular oxidative addition of apolar σ-bonds to Au(I), using diphosphine ligands bearing Si—Si and Sn—Sn bonds (Figure 8a).[45] Remarkably, when using the corresponding monophosphine-disilane ligand, the oxidative addition of the σ-Si—Si bond at gold(I) also occurred.[45c] In all cases, the resulting bis(silyl)- and bis(stannyl)gold(III) complexes were characterized. In addition, the oxidative addition of σ-Si—Si bonds could be expanded to an intermolecular regime by reacting phosphine gold(I) chloride complexes with disilanes in the presence of GaCl₃ at low temperature, as a proof of concept that oxidative addition of the σ-Si—Si bond can take place directly at Au(I) without requiring chelating assistance (Figure 8b). The resulting Au(III) complexes featured an unusual, distorted Y shape and were unstable above −60 °C or even −80 °C depending on the phosphine.[46] In 2014, the group of Toste designed a Au(I)-aryl complex with a tethered allyl bromide arm that underwent oxidative addition of the C-(sp3)—Br bond to the Au(I) center under mild conditions (Figure 8c). The resulting Au(III) complex served as a mechanistic proof for the oxidant-free gold-catalyzed allylation of arylboronic acids presented in the same work.[47] Also in 2014, Amgoune, Bourissou and coworkers reported the intramolecular oxidative addition of C(sp2)—X bonds (X = Br, I) to Au(I). The design of the 8-halonaphtyl phosphine ligands suitably places the C(sp2)—X bond close to the Au(I) atom when it is coordinated to the phosphine moiety, inducing the stabilization of the (P,C)-cyclometalated Au(III) products obtained upon
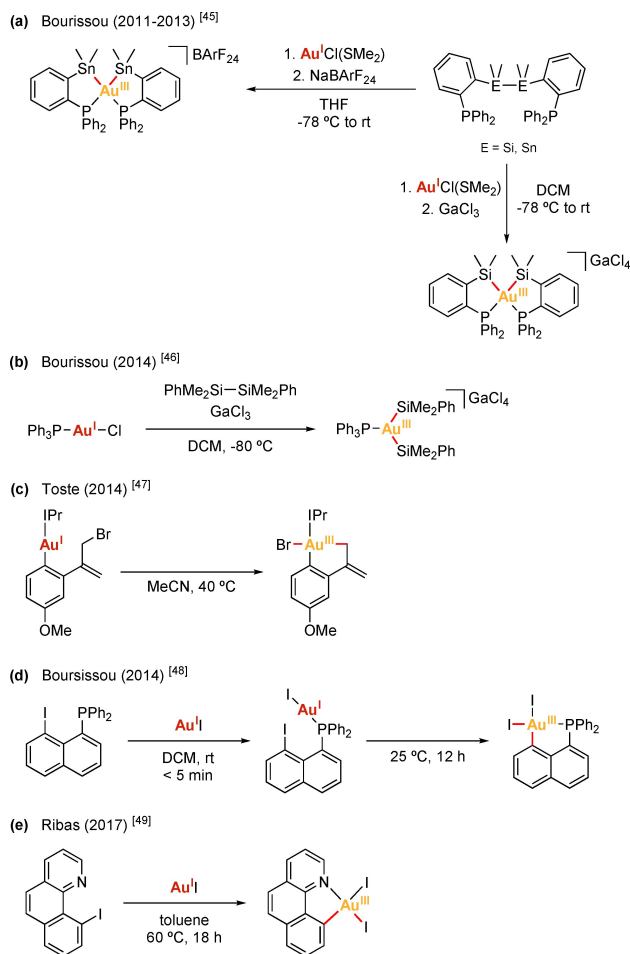

Figure 8. Selected examples of intramolecular chelation-assisted oxidative addition at Au(I) (**a**, **c–e**), and intermolecular oxidative addition of disilanes at a phosphine gold(I) chloride complex (**b**).

oxidative addition (Figure 8d).[48] Additionally, the authors also prepared PCP-pincer Au(III) complexes via oxidative addition of a C(sp2)—Br bond when employing a bromophenyl diphosphine ligand, by means of the same strategy. In 2017, Ribas and coworkers generated a (N,C)-cyclometalated Au(III) complex via oxidative addition by reacting gold(I) iodide and 10-iodobenzo [h]quinoline under moderate heating (Figure 8e).[49]

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Bidentate ligands with small bite angles. The design of bidentate ligands featuring a bite angle smaller than 180° when chelating gold(I) centers has also showed efficiency at rendering Au(III) species via oxidative addition. The preorganization of the non-linear Au(I) complex reduces the deformation energy required to become a square-planar Au(III) complex.

In 2014, Amgoune, Bourissou and coworkers applied this strategy using carborane diphosphine ligands (DPCb) that chelate the gold(I) atom with P—Au—P angles between 90° and 100° depending on the counterion. The authors could activate C(sp2)-I bonds from several aryl iodides at room temperature affording well-defined aryl-Au(III) complexes that could be isolated and fully characterized (Figure 9a).[50] Intriguingly, the oxidative addition of *p*-substituted iodobenzenes occurred faster with more electron-rich arenes, featuring the opposite reactivity trend to the one observed in isoelectronic L2Pd(0) complexes undergoing oxidative addition of aryl halides.[51] In 2015, the same group combined the use of bent [(DPCb)Au(I)]+ complexes with the strain release strategy to promote the oxidative addition of the strained C—C bonds in biphenylene and in benzocyclobutenone (Figure 9b).[52] The oxidative addition of benzocyclobutenone afforded two acyl-gold(III) complexes upon selective activation of either the C(aryl)-C(O) bond (kinetic product) or the C(alkyl)-C(O) bond (thermodynamic product), by adjusting the reaction conditions. Remarkably, the oxidative addition of the C(aryl)—C(O) bond turned to be

reversible since the isolated kinetic product, when in solution, evolved slowly back to the cationic Au(I) complex and, over time or upon heating, the thermodynamic acyl-Au(III) complex was formed.

In 2018, Russell and coworkers reacted a three-coordinated 2,2'-bipyridyl-chelated gold(I) ethylene complex, featuring a N—Au—N angle of 74.57°, towards the reversible oxidative addition of C(sp2)-I bonds in different aryl iodides (Figure 9c).[53] Electron-rich aryl iodides reacted faster than electron-poor ones, showing a reactivity trend that agrees with the previously reported by Bourissou.[50] In 2020, Russell reported the first examples of intermolecular oxidative addition of alkenyl and alkynyl iodides to the same Au(I) complex, forming alkenyl Au(III) complexes in a reversible and stereospecific manner for the former (Figure 9c).[54]

Hemilabile ligands. In 2016, Bertrand and coworkers reported a (CAAC)AuCl complex (CAAC=Cyclic Alkyl Amino Carbene) bearing a pendant hemilabile imine moiety that helped at stabilizing the Au(III) complex obtained upon oxidative addition of the strained C—C bond in biphenylene (Figure 10a).[55] One year later, the group of Bourissou employed the di(1-adamantyl)-2-dimethylaminophenylphosphine (MeDalphos) ligand in (MeDalphos)AuCl, a phosphine ligand with a hemilabile tertiary amine, to stabilize the (P,N)-cyclometalated Au(III) species resulting from the oxidative addition of the strained C—C bond in biphenylene and the C—X bonds in
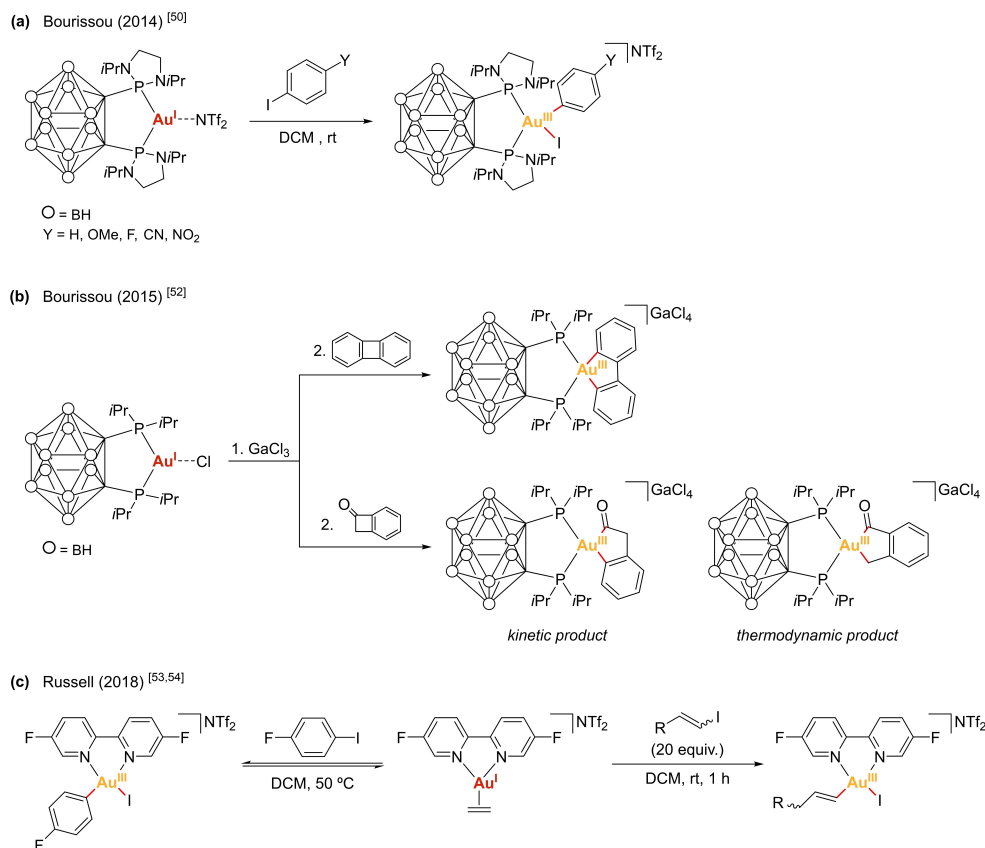

(a) Bourissou (2014) [50]

O = BH
Y = H, OMe, F, CN, NO2

(b) Bourissou (2015) [52]

O = BH

kinetic product   thermodynamic product

(c) Russell (2018) [53,54]

Figure 9. Selected examples of non-linear gold(I) complexes that are preorganized to undergo oxidative addition under mild conditions.

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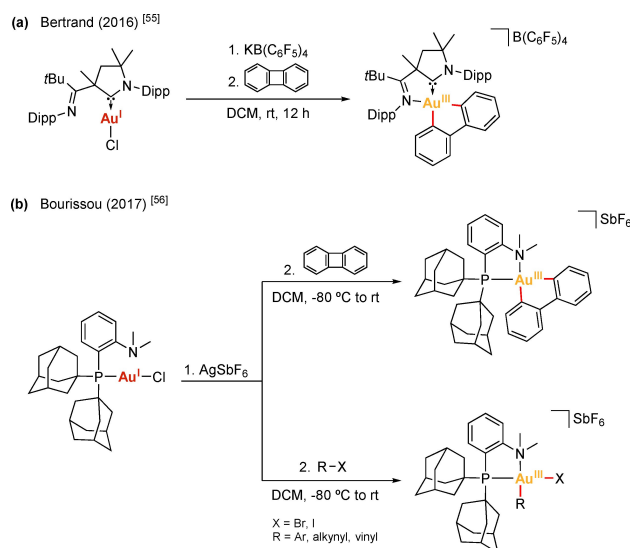European Chemical Societies Publishing

Figure 10. Selected examples of hemilabile ligand-stabilized aryl-Au(III) complexes obtained via oxidative addition.

iodoaryls, bromoaryls, alkynyl iodides and vinyl iodides (Figure 10b).[56] In line with these works, in 2021, the group of Nevado used different (P,N)-[(MeDalphos)Au(III)(Ar)(I)]$^+$ complexes, obtained via oxidative addition, to further explore their chemistry and included some variations at the ligand, such as replacing the adamantyl substituents by *tert*-butyls and replacing the dimethylamino group by a piperidinyl unit.[57] In addition, Spokoyny and coworkers also used (MeDalphos)AuCl to synthesize a wide library of Au(III) complexes of the type (P,N)-[(MeDalphos)Au(III)(Ar)(X)]SbF$_6$ (X = I, Cl) via oxidative addition.[58] These complexes served as robust arylation reagents in a general protocol for cysteine S-arylation of unprotected peptides and proteins. Further, in 2021 the same group used the *tert*-butyl-substituted version of the MeDalphos ligand to develop (P,N)-gold(III) platforms that work as efficient and selective cysteine arylation reagents, giving access to arylated bioconjugates of higher structural complexity including bicyclic peptides, stapled peptides and peptide-functionalized hybrid nanoclusters.[59]

2.3. Photochemical Conditions to Promote Oxidative Addition at Au(I)

A surrogate strategy to access Au(III) species within Au(I)/Au(III) catalytic cycles avoiding external oxidants is the use of photochemical conditions that allow the oxidative addition, generally of diazonium salts, under mild conditions to obtain well-defined aryl-Au(III) complexes.

In 2016, the group of Hashmi reported the oxidative addition of aryldiazonium salts to phosphine- and NHC-gold(I) complexes promoted by the irradiation with blue light LEDs.[60] When using chelating (P,N)-ligands, cationic five- and six-membered chelate gold(III) complexes were obtained, whereas when using monodentate phosphine ligands and NHC ligands,

the corresponding neutral Au(III) complexes were formed. Also in 2016, Glorius and coworkers developed a straightforward approach towards well-defined cationic (N,C)-cyclometalated Au(III) complexes via photoredox-promoted oxidative addition of aryldiazonium salts to LAuCl complexes (L = phosphine or NHC), in the presence of a Ru photocatalyst under irradiation of green LEDs at room temperature (Figure 11a).[61] Alternatively, Porcel and coworkers employed in situ generated aryldiazonium salts as electrophiles that oxidatively added to LAuCl complexes (L = PPh$_3$ or SMe$_2$) under thermal conditions, without requiring photochemical conditions.[62] The ensuing arylgold(III) complexes could be isolated and characterized.

In 2014, Toste and coworkers reported the oxidative addition of CF$_3$I to phosphine Au(I) aryl complexes via a photoinitiated radical chain reaction. The use of near-ultraviolet light promoted the excitation of CF$_3$I to end up with Au(III) complexes of the type (PR$_3$)Au(aryl)(CF$_3$)(I) that could be isolated and characterized (Figure 11b).[63] In 2019, the same group isolated Au(III) complexes from the photoredox-initiated arylation of (IPr)AuX complexes (X = CF$_3$ or succinimide), using aryldiazonium salts, a Ru-based photoredox catalyst and blue light LED irradiation (Figure 11c).[64] The authors claimed a radical chain oxidative addition in which the ruthenium catalyst first generates an aryl radical that adds to the Au(I) complex. Then, the resulting arylgold(II) species undergoes a single electron oxidation by reacting with the aryldiazonium salt. This reaction generates an arylgold(III) species that could be isolated in coordinating solvents.

3. Oxidant-Free Au(I)/Au(III) Cross-coupling Catalysis

Oxidative addition at gold(I) can unequivocally be achieved if proper conditions are provided, as revised in the approaches described in sections 2.1 - 2.3. The combination of oxidative addition with other fundamental organometallic transformations is key for designing synthetic methodologies proceeding through oxidant-free two-electron redox Au(I)/Au(III) catalytic cycles. In this section, the attention will be focused on cross-coupling catalysis operating via Au(I)/Au(III) cycles in the absence of external oxidants.[65]

3.1. Substrate and Ligand Design for the Development of Au(I)/Au(III) Catalytic Cycles

In 2014, Toste and coworkers used a bis(diphenylphosphino)amine ligand-supported bimetallic Au(I) complex to catalyze the allylation of arylboronic acids.[47] Interestingly, the analogous monometallic aminophosphine Au(I) complex afforded the C(sp2)—C(sp3) coupling products in much lower yields, suggesting that the bimetallic catalyst structure enhances the catalytic activity. The oxidative addition of allyl bromides to the bimetallic Au(I) aryl complex was suggested to be the key step of the catalytic cycle, and a bimetallic Au(II)-Au(II) species was
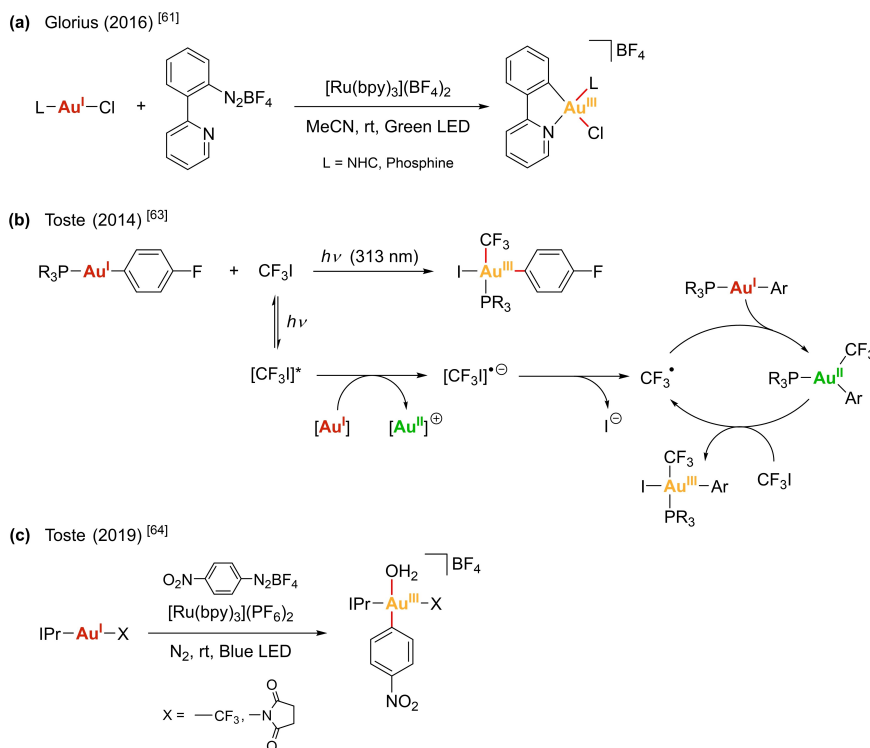
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Figure 11. Selected examples of aryl-Au(III) complexes obtained via oxidative addition promoted by photochemical conditions.

proposed to be formed rather than discrete Au(III). They supported the viability of the oxidative addition of the allylic C(sp3)—Br bond to Au(I) under intramolecular conditions (see Figure 8c).

The group of Ribas designed Au(I)/Au(III)-catalyzed cross-coupling transformations taking advantage of the chelation-assisted strategy. In 2015, they reported the halide exchange and C(sp2)—O bond-forming reactions employing a cationic NHC—Au(I) complex and model aryl halide triazamacrocyclic substrates.[66] The latter had previously demonstrated to be convenient substrates for the stabilization of Cu(III) and Ag(III) intermediates obtained via oxidative addition in Cu(I)/Cu(III)- and Ag(I)/Ag(III)-catalyzed C—C and C—X bond-forming cross-couplings.[16a,d,e,67] In this work, the authors also could extrapolate the halide exchange and the C(sp2)—O coupling reactions to 2-(2-halophenyl)pyridines, i.e. substrates bearing a single chelating group. The detection of Au(III) intermediates was not possible neither using the triazamacrocyclic substrates nor the 2-(2-halophenyl)pyridines. However, a Au(I)/Au(III) catalytic cycle was postulated and supported by DFT studies.[66] In 2017, the same group reported oxidant-free C(sp2)—O and C(sp2)—N coupling reactions catalyzed by the same cationic NHC—Au(I) complex employing 2-(2-halophenyl)pyridines as substrates.[49] Interestingly, the intermediacy of Au(III) species could be validated when using 10-iodobenzo[h]quinoline, evidencing that a more rigid and flat chelating substrate stabilizes better the Au(III) species formed upon oxidative addition (Figure 12).

In line with the use of hemilabile bidentate ligands, Bourissou and coworkers employed the (P,N)-MeDalphos ligand
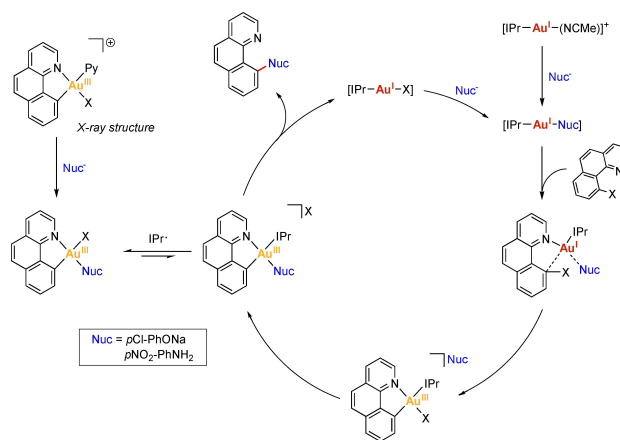

Figure 12. Proposed mechanism for the oxidant-free Au(I)/Au(III)-catalyzed C(sp2)—O and C(sp2)—N cross-coupling reported by Ribas and coworkers.[49]

to develop the Au(I)/Au(III)-catalyzed cross-coupling between aryl halides and electron-rich arenes to afford biaryls under mild conditions (Figure 13a).[56a] The catalytic cycle was shown to proceed following the C(sp2)—X oxidative addition/C(sp2)—H auration/reductive elimination sequence. The great performance of MeDalphos ligand at stabilizing Au(III) intermediates paved the way to envision new Au(I)/Au(III) catalytic transformations using the (MeDalphos)AuCl catalyst. In this regard, in 2019 Bourissou and coworkers reported the regioselective C3 arylation of indoles, which is rarely observed by means of other transition metal-mediated catalysis (Figure 13b).[68] Moreover, it
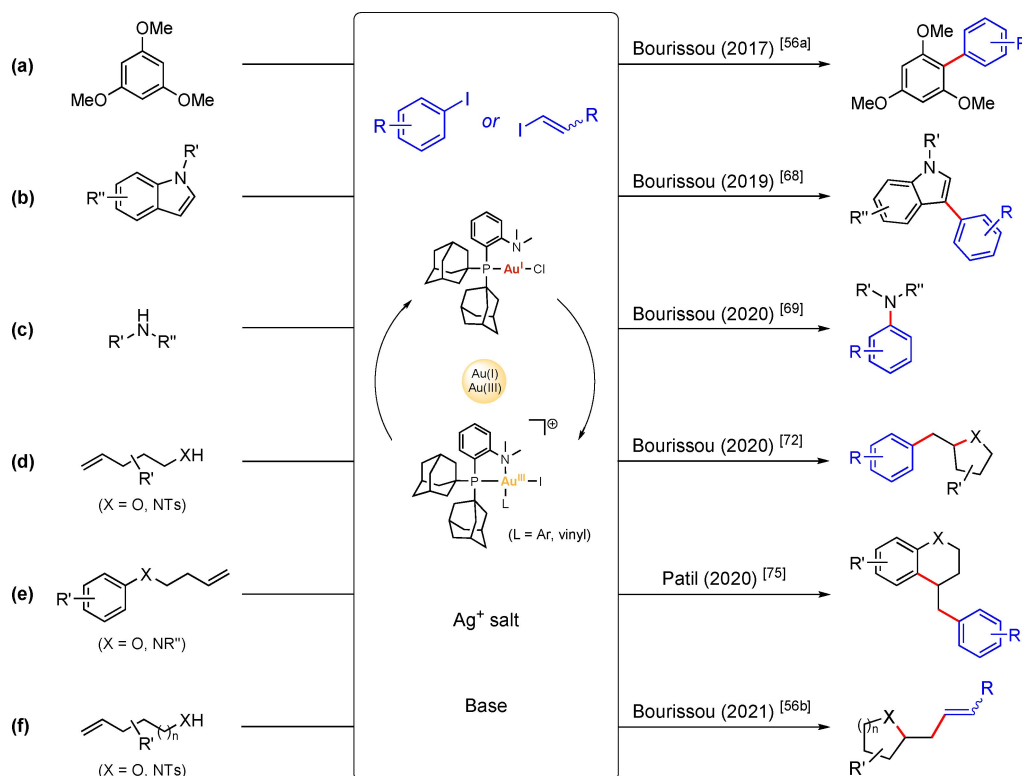
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Figure 13. Au(I)/Au(III) cross-coupling catalysis enabled by MeDalphos ligand.

displayed a high functional group tolerance at both the iodoarene and indole partners. In 2020, the same group used the (MeDalphos)AuCl catalyst in C(sp2)—N cross-coupling reactions (Figure 13c).[69] They developed a robust and mild methodology for coupling a wide scope of aryl iodides and N-nucleophiles under mild conditions. The reaction mechanism was thoroughly investigated, including the characterization of a key Au(III) intermediate. Patil and coworkers also contributed, independently, to the development of C(sp2)—N cross-coupling of aryl iodides with amines mediated by the MeDalphos-enabled Au(I)/Au(III) catalysis.[70]

Further, Bourissou and coworkers had already demonstrated the ability of MeDalphos ligand to stabilize gold(I) π-complexes,[71] besides its capability to promote Au(I)/Au(III) two-electron redox transformations. Therefore, the same group took advantage of the great performance of MeDalphos ligand to develop the oxy- and aminoarylation of alkenols and alkenamines by means of Au(I)/Au(III) catalysis that combines oxidative addition of aryl iodides with π-activation of olefins (Figure 13d).[72] This strategy proved suitable to access products with 5-, 6- and 7-membered rings and electron-rich aryl substrates reacted readily. Likewise, the group of Patil also employed the MeDalphos ligand to synthesize 1,2-oxy- and 1,2-aminoarylation products from the coupling of aryl iodides with alkenes.[73] In the case of oxyarylations, two- and three-component reactions were reported, whereas aminoarylations were only carried out as two-component reactions. The 1,2-aminoarylations of alkenes were also shown to proceed by

reacting alkenes tethered to aryl iodide moieties with external amines.[74] The use of MeDalphos ligand allowed the same group to develop, as well, the first ligand-enabled Au(I)/Au(III)-catalyzed 1,2-diarylation of alkenes by merging the oxidative addition of aryl iodides to Au(I) with π-activation of alkenes (Figure 13e).[75] In this case, the mechanism was proposed to involve an aromatic electrophilic substitution (S_EAr) step for the carboauration of alkenes. The resulting Au(III)-aryl-alkyl intermediate could be detected by means of mass spectrometry. Notably, the selective reactivity disclosed in this work avoids the formation of undesired Ar—Ar' and Heck-type byproducts observed in other transition metal catalysis. More recently, the group of Bourissou applied the oxidative addition of vinyl iodides to (MeDalphos)AuCl in catalysis, in combination with π-activation, to develop oxy- and amino-vinylation reactions using alkenols and N-tosyl alkenamines, respectively (Figure 13f).[56b]

3.2. Coupling Partners with Dual Role

The use of diazonium salts, which act dually as coupling partners and as oxidizing equivalents, has led to a wide scope of oxidant-free gold redox coupling catalysis. For instance, in 2015 Chen, Shi and coworkers reported the C(sp)—C(sp2) and C(sp2)—C(sp2) cross-coupling between aryldiazonium salts and terminal alkynes or arylboronic acids, respectively. In this case, the addition of a bipyridine auxiliary ligand was key to assist nitrogen extrusion.[76] In 2016, the same group reported the

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gold-catalyzed C—Br, C—S and C—P Sandmeyer couplings between aryldiazonium salts and the corresponding nucleophiles.[77] Crucial to the success of this transformation was the nucleophile-assisted activation of aryldiazonium salts, which were then added to Au(I) to yield Au(III) intermediates. In 2017, Shi reported the Lewis base-assisted diazonium activation as a strategy to access gold oxidation and build a Au(I)/Au(III) catalytic cycle for the intramolecular oxy- and aminoarylation of alkenes, the arylative ring expansion of alkenes, the oxy- and aminoarylation of allenes, and the propargyl ester rearrangement of alkynes.[78] Additionally, in 2018 the group of Dughera reported the gold-catalyzed Heck and Suzuki-Miyaura couplings using arenediazonium o-benzenedisulfonimides as electrophilic partners.[79] They proposed a Au(I)/Au(III) catalytic cycle that did not require the presence of external oxidants since the o-benzenedisulfonimide anion was suggested to act as an electron transfer agent that promoted the oxidation to Au(III) intermediate species via a radical pathway. Intriguingly, in 2018, Patil and coworkers reacted aryldiazonium salts with diverse organostannanes towards the formation of biaryls, vinyl arenes and arylacetylenes via Au(I)/Au(III) cross-coupling at mild conditions.[80] In 2019, Shi and coworkers reported the cyclization-arylation of allylic oximes to access aryl functionalized 2-isoxazolines in good yields.[81] The reaction occurred via chemical activation of the diazonium salt. The use of Li_2CO_3 as a base assisted the N_2 extrusion to promote the oxidation of Au(I) to Au(III) aryl species while slowing down the aryl radical generation, which otherwise decomposed the oxime substrate.

Light irradiation, however, has proved useful to promote the activation of aryldiazonium salts, which can then add to Au(I) giving access to Au(I)/Au(III) catalytic cycles. Several groups have worked on the synthesis of (hetero)biaryls by means of photosensitizer-free light-induced gold redox catalysis, such as Bandini, who worked on the Suzuki coupling of arylboronic acids with arylazosulfones (Figure 14a),[82] or Hashmi, who worked on the coupling of aryldiazonium salts with organoboron and organosilicon reagents (Figure 14b).[83] In 2016, Hashmi and coworkers reported the visible-light-mediated gold-catalyzed intermolecular 1,2-difunctionalization of alkynes with aryldiazonium salts in methanol to afford α-aryl ketones.[84] In 2017, the group of Wong reported the light-mediated gold-catalyzed cis-difunctionalization of silyl-substituted alkynes with quinoline-substituted aryldiazonium salts in high chemo- and regioselectivity.[85] Interestingly, in 2019, Hashmi and coworkers reported a study in which the Au-catalyzed reaction of o-alkynylphenols with aryldiazonium salts led to different outcome depending on whether blue LED light was applied or not, under the same reaction conditions.[86] Under blue LED irradiation, N_2 extrusion from the diazonium salt was promoted and arylated benzofurans were formed, whereas in the absence of a light source, the N_2 unit was retained and azobenzofurans were obtained. In 2020, Feng and coworkers reported the visible-light-promoted gold redox catalysis for the regio- and stereoselective fluoroarylation of allenic esters.[87]

Ethynylbenziodoxolone reagents (EBX), which can be regarded as electrophilic alkyne surrogates, have also been used as reagents that play the dual role as coupling partners and oxidants. In 2013, Waser and coworkers reported the domino cyclization/alkynylation reaction of allenic ketones with EBXs to afford C3-alkynylated furans, employing a Au(III) catalyst (Figure 15a).[88] Computational studies on the mechanism of this domino reaction revealed that the Au(III) catalyst was the precursor of the active Au(I) catalyst that initiates the Au(I)/Au(III) catalytic cycle.[89] In 2017, Patil and coworkers reported the gold-catalyzed C(sp)—C(sp) alkynylation of terminal alkynes with EBXs to access unsymmetric 1,3-diynes (Figure 15b).[90] They used Ph_3PAuCl as catalyst and catalytic amount of 1,10-phenanthroline as auxiliary ligand. Likewise, the group of Liu also used alkynyl hypervalent iodine reagents in the coupling with terminal alkynes for the synthesis of unsymmetrical 1,3-diynes.[91]

3.3. Photoredox-Gold Dual Catalysis

Despite the abovementioned examples of gold-catalyzed couplings under photosensitizer-free conditions or operating via light-assisted activation of aryldiazonium salts, many studies have relied on dual photoredox-gold catalytic systems to develop a wide array of synthetic strategies.[92] The combination of homogeneous gold catalysis and photoredox catalysis consists of a photocatalyst that, once excited by light irradiation, generates an organic radical (generally an aryl
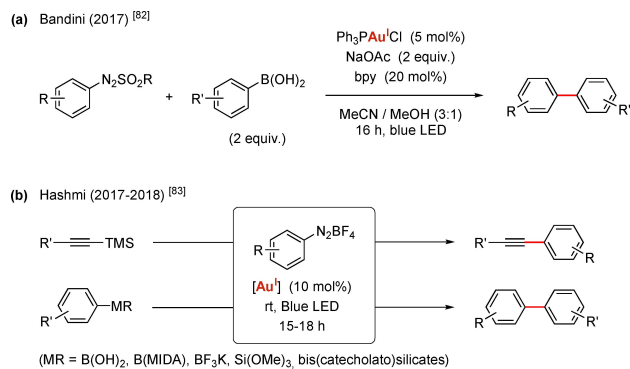
Figure 14. Au(I)/Au(III) cross-coupling catalysis of aryldiazonium salts with organoboron and organosilicon reagents under light irradiation.
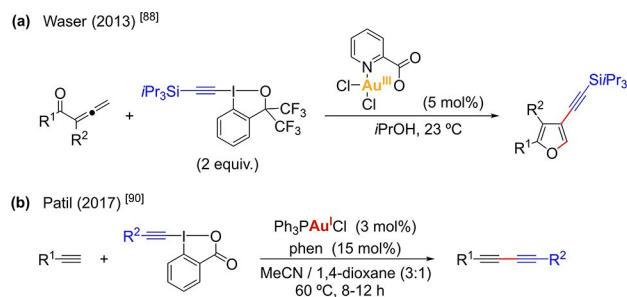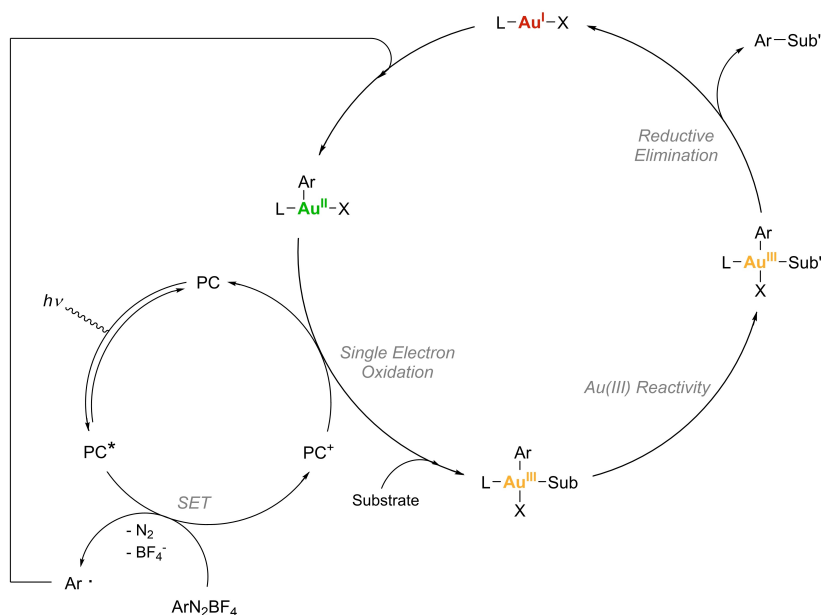
Figure 15. Selected examples of Au(I)/Au(III) cross-coupling catalysis involving EBX reagents as coupling partners.

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radical from aryldiazonium salts) via single electron transfer while getting itself oxidized (Figure 16a). The organic radical can add to Au(I) to give a transient gold(II) species which subsequently undergoes oxidation to Au(III) while regenerating the ground-state photocatalyst via single electron transfer. Finally, reductive elimination from Au(III) affords the coupling product and Au(I).
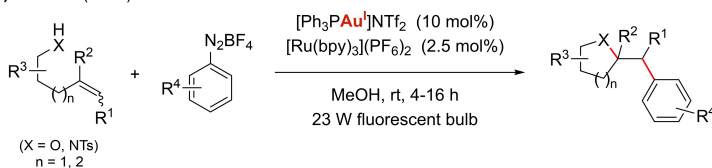
In 2013, Glorius and coworkers reported for the first time a dual photoredox gold catalytic system for the intramolecular oxy- and aminoarylation of alkenes with aryldiazonium salts, at room temperature under the irradiation of a fluorescent light bulb, with the assistance of the $[Ru(bpy)_3](PF_6)_2$ photocatalyst (Figure 16b).[93] Frei and Toste developed the arylative ring expansion of alkenyl and allenyl cycloalkanols by coupling them with aryldiazonium salts, to afford cyclic ketones (Figure 16c).[94] The reaction was promoted by visible light photoredox catalysis and gold catalysis at room temperature. Mechanistic studies let the authors propose that the electrophilic Au(III)-aryl intermediate reacted towards the π-bonds of the substrates to undergo ring expansion and reductive
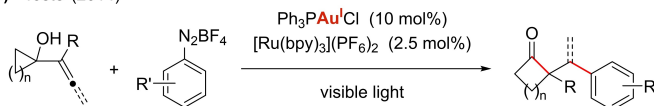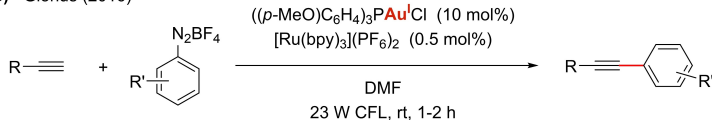

Figure 16. General mechanistic scheme of photoredox-gold dual catalysis and selected examples using aryldiazonium salts as coupling partners.

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elimination. Toste and coworkers, one year later, used the dual photoredox gold catalysis approach to develop the C(sp2)–P coupling between aryldiazonium salts and H-phosphonates under visible light irradiation at room temperature (Figure 16d).[95] Glorius and coworkers developed the arylation of terminal alkynes using aryldiazonium salts. The reaction was mediated by visible light from a household bulb or sunlight at room temperature and was run in the absence of base. Thus, it stands as the first example of achieving C–H activation by means of dual gold photoredox Au(I)/Au(III) catalysis (Figure 16e).[96] The group of Lee reported the first aryl-aryl cross-coupling via direct C–H activation under a dual photoredox gold catalytic fashion under blue LED light irradiation.[97] In 2016, independent groups reported tandem Meyer-Schuster/ arylation reactions for the synthesis of α-arylated enones, under dual photoredox gold catalysis.[98] Kim and Toste, more recently, provided mechanistic support for the formation of Au(III) intermediates in dual photoredox gold processes.[64] Particularly, they validated the formation of Au(III) species via photoredox-initiated arylation of (IPr)Au(I)–CF₃ and (IPr)Au(I)–succinimide using 10 mol% [Ru(bpy)₃](PF₆)₂ (see Figure 11c) and confirmed that C(sp2)–CF₃ and C(sp2)–N coupling products were obtained via subsequent reductive elimination.

The scope of compatible coupling partners in dual photo-redox gold catalysis does not only rely on the employment of aryldiazonium salts. In 2017, the group of Xu aimed to expand the scope by reporting an unprecedented intermolecular thiosulfonylation of alkenes with excellent regio- and diastereoselectivity (Figure 17a).[99] They reacted styrenes with PhSO₂SR reagents, using (IPr)AuCl as catalyst, AgSbF₆, and [Ru(bpy)₃]Cl₂ as photocatalyst at room temperature under visible light. In 2019, Fensterbank and coworkers reported the alkynylative cyclization of o-alkynylphenols with iodoalkynes under visible light irradiation to access alkynylbenzofuran derivatives (Figure 17b).[100] They claimed that the iridium(III) photocatalyst triggered the oxidative addition of the alkynyl iodide coupling partner onto an excited vinylgold(I) intermediate obtained by energy transfer from the excited iridium photocatalyst. The C(sp2)–C(sp) coupling products were obtained via subsequent reductive elimination.
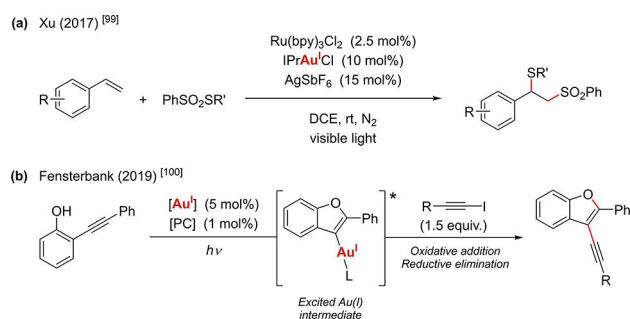

Figure 17. Dual photoredox gold-catalysis for (a) the thiosulfonylation of alkenes and (b) photosensitized oxidative addition to Au(I) in the alkynylative cyclization of o-alkynylphenols with iodoalkynes.

4. Conclusions

Gold catalysis is entering a new dimension through the development of external oxidant-free Au(I)/Au(III) catalytic protocols for C–C and C-heteroatom cross coupling reactions. The dedicated design of hemilabile ligands excels among other strategies to achieve the stabilization of Au(III) intermediate species upon oxidative addition with aryl halides, and the desired catalytic turnover. In this line, the P,N bidentate MeDalphos ligand stands as the most successful example. Moreover, the use of diazonium salts coupled with light irradiation in the absence or presence of photosentizisers is another successful strategy at front line of Au(I)/Au(III) that does not require external oxidants. We envision a bright and shiny golden future for this line of research.

Conflict of Interest

The authors declare no conflict of interest.

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