Oxidant speciation and anionic ligand effects in the gold-catalyzed oxidative coupling of arenes and alkynes

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Abstract: The mechanism of the gold-catalyzed oxidative cross-coupling of arenes and alkynes has been studied in detail combining stoichiometric experiments with putative reaction intermediates and DFT calculations. Our data suggest that ligand exchange between the alkyne, the Au(I)-catalyst and the hypervalent iodine reagent is responsible for the formation of both, a Au(I)-acetylide complex as well as a more reactive “non-symmetric” I(III) oxidant, responsible for the crucial Au(I)/Au(III) turnover. Further, the reactivity of the in situ generated Au(III)-acetylide complex is governed by the nature of the anionic ligands transferred by the I(III) oxidant: while halogen ligands remain unreactive, acetato ligands are efficiently displaced by the arene to yield the observed Csp2-Csp cross-coupling products through an irreversible reductive elimination step. Finally, the nature of competitive processes and catalyst deactivation pathways has also been unraveled. This detailed investigation provides insights not only on the specific features of the species involved in oxidative gold-catalyzed cross couplings but also highlights the importance of both ancillary and anionic ligands on the reactivity of the key Au(III) intermediates.

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Oxidant Speciation and Anionic Ligand Effects in the Gold-catalyzed Oxidative Coupling of Arenes and Alkynes

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The mechanism of the gold-catalyzed oxidative cross-coupling of arenes and alkynes has been studied in detail combining stoichiometric experiments with putative reaction intermediates and DFT calculations. Our data suggest that ligand exchange between the alkyne, the Au(I)-catalyst and the hypervalent iodine reagent is responsible for the formation of both, a Au(I)-acyclyl complex as well as a more reactive “non-symmetric” I(III) oxidant, responsible for the crucial Au(I)/Au(III) turnover. Further, the reactivity of the in situ generated Au(III)-acyclyl complex is governed by the nature of the anionic ligands transferred by the I(III) oxidant: while halogen ligands remain unreactive, acetato ligands are efficiently displaced by the arene to yield the observed Csp²-Csp cross-coupling products through an irreversible reduction elimination step. Finally, the nature of competitive processes and catalyst deactivation pathways has also been unraveled. This detailed investigation provides insights not only on the specific features of the species involved in oxidative gold-catalyzed cross couplings but also highlights the importance of both ancillary and anionic ligands on the reactivity of the key Au(III) intermediates.

Scheme 1. Au-Catalyzed Alkynylation of Arenes

In the catalytic version, a hypervalent iodine reagent was selected as oxidant on the basis of significant evidence that these species could promote Pd(II)/Pd(IV) catalytic cycles. We thus anticipated that a Au(I)/Au(III) catalytic turnover could be implemented under the reaction conditions. Furthermore, the ability of Au(III) species to trigger Csp²-H activation in electron rich arenes is also well established. Although Au(I)/Au(III)-catalyzed reactions have recently emerged as powerful tools for C-C cross couplings, with few notable exceptions, the mechanistic understanding of these processes is still limited and the characterization of putative intermediates scarce. We report herein a detailed investigation aiming to elucidate the factors governing both, reactivity and selectivity in these transformations.

In our previous work, the mechanistic rationale involved: (i) an equilibrium between the free alkyne and the Au catalyst with the aid of base to form a Au(I)-acyclyl complex (I); (ii) oxidation of I with Phl(OAc)₂ to form Au(III) species II; (iii) an arenne auration to produce intermediate III which evolves via reductive elimination (iv) yielding

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Introduction

 Aryl alkynes have found widespread use as building blocks in the synthesis of numerous natural products, bioactive molecules and organic materials. In recent years, metal-catalyzed Csp²-H bond functionalizations have been explored as an alternative strategy to classical Pd-catalyzed cross-coupling reactions for the efficient construction of Csp²-Csp bonds. These approaches are attractive because they avoid the otherwise necessary pre-functionalization of the aromatic partner. However, and in contrast to the large body of metal-catalyzed Csp²-H arylation reactions, the direct Csp²-H alkynylation of arenes has been much less explored. Few examples though have shown the viability of this strategy. In 2010, the Cu-catalyzed direct alkynylation of electron deficient polyfluoroarenes with terminal alkynes using O₂ as oxidant was reported by Su et al. Despite its efficiency, the reaction is barely catalytic and relies on the acidity of the Csp²-H bond in the arene substrate. A different approach focused on the stoichiometric use of alkynylidonium species as an electrophilic source of acetylenic moieties in the presence of catalytic amounts of late transition metals as demonstrated by Waser et al. In this context, our group reported an oxidative alkynylation of arenes via Au-catalyzed C-H functionalization of both Csp- and Csp²-H bonds (equation 1, Scheme 1). One of the most remarkable features of this protocol was the use of “deactivated” electron rich arenes and electron deficient alkynes as coupling partners. A catalytic amount of Ph₃PAuCl in combination with commercially available PhI(OAc)₂ as stoichiometric oxidant was found to be effective in producing Csp²-Csp bonds. A stoichiometric version of this transformation had been already described by Fuchita and co-workers back in 2001.
product IV (Scheme 2, path A.1). Alternatively, in line with Waser’s reports on the stoichiometric use of alkynyliodonium salts, a ligand exchange between PhI(OAc)₂ and Au(I)-acetylide (I) to give an alkynyliodonium intermediate (V) could also be proposed. Arene addition to give VI followed by θ-Gu elimination would then furnish product IV as shown in path B.1 of Scheme 2. Alternatively, transmetallation between alkynyliodonium salt V and putative aryl-Au(III) species (VII) produced in situ within the oxidative reaction media could also deliver intermediate III, which would yield the observed products after reductive elimination as shown in Scheme 2, path B.2.

**Scheme 2. Plausible Mechanisms for Au-Catalyzed Alkynylation of Arenes**

Our preliminary study left opened several key questions: first and foremost, the role of PhI(OAc)₂ needed to be established, whether it functioned as a stoichiometric oxidant to achieve the Au(I)/Au(III) turnover or as an electrophilic source to exchange and then cross-couple the alkyne to an electron rich arene, or both. In addition, the order of steps needed to be clarified as to whether the transfer of the alkyne to the gold(I) complex (path A.1) or a direct oxidation (path A.2) was involved in the initial step of the catalytic cycle. Furthermore, neither detailed information about the metal coordination sphere in the proposed Au(III) intermediates II and III nor about the oxidant environment was available from these initial investigations.

**Results and Discussion**

Initial experiments to investigate the feasibility of pathways B.1 and B.2 focused on alkynyliodonium salts (V) in order to reveal their potential role as intermediates in these transformations.

**Figure 1. a-d) Stoichiometric experiments involving alkynyliodonium species (path B.1 and B.2 in Scheme 2). e-f) Stoichiometric experiments regarding path A.2.**

Treatment of methyl 3-phenyl(tosyloxy)-(3-iodanyl)propiolate with stoichiometric amounts of 3,5-dimethoxytoluene (4) and Ph₃PAuCl or Ph₃PAuOAc at 90 °C did not furnish the desired Csp²-Csp cross coupling product and only decomposition of the alkynyliodonium salt was detected (Figure 1a, 1b). Identical experiments in the presence of gold(III) complexes like Ph₃PAuCl₃ or Au(OAc)₃/PPH₃ showed a similar outcome (Figure 1c, 1d). Interestingly, in case of Ph₃PAuCl₃ formation of 2-chloro-1,5-dimethoxy-3-methylbenzene as by-product could be observed. These control experiments (Section 2 in the SI) led us to rule out pathways B.1 and B.2 and the participation of alkynyliodonium species V as intermediates in these transformations.

Experiments to investigate pathway A.2 involved the participation of the alkyne in presence of gold(III) species. However, stoichiometric experiments of 3,5-dimethoxytoluene (4), methyl propiolate (5) and Ph₃PAuCl or Au(OAc)₃/PPH₃ at 90 °C showed the formation of the arylchloride in case of Ph₃PAuCl but no participation of the alkyne (Figure 1e, 1f). To explore the direct oxidation of the initial catalyst, Ph₃PAuCl was treated with excess of PhI(OAc)₂ at 90 °C. However, no reaction was observed even after prolonged heating and just Ph₃PO could be detected in trace amounts (Figure S2-3 in the SI). These experiments suggest that the neutral Ph₃PAuCl complex used as catalyst is scarcely oxidized by PhI(OAc)₂ under the reaction conditions, in contrast to previous results obtained for PhICl₂ which furnished Ph₃PAuCl₂ in 96% yield even at room temperature. In situ oxidation of the Au(I) catalyst also seems to be at the outset of the Au-catalyzed oxidative oxo- and aminoarylation of alkenes with boronic acids. However, the results described herein clearly indicate that the present alkynylation reaction proceeds, at least on the outset, through an alternative reaction mechanism.

**Formation and Reactivity of Au(I)-acetylide (8)**

To investigate path A.1, a careful spectroscopic analysis (¹H and ³¹P NMR) of the reaction mixture stemming from the reaction between 3,5-dimethoxytoluene (4) and methyl propiolate (5) under the standard conditions (5 mol% Ph₃PAuCl, 1.5 equiv. PhI(OAc)₂, 1 equiv. NaHCO₃) was performed. The reaction showed the presence of three species: the initial catalyst Ph₃PAuCl, [Ph₃P₂]AuCl (7) and a Ph₃PAuCl₂(C(C₁=C₃)₂Me) complex (8) (Figure 2a and S4-5 in the SI). Complex 8 appears already after the first minutes of the reaction and it disappears towards the end whereas Ph₃PAuCl and 7 are present after the starting materials have been completely consumed. Ph₃PO could not be detected in the reaction mixture. These results indicate that the phosphine ligand remains bound to the metal center and thus does not get oxidized by PhI(OAc)₂ in appreciable quantities. In situ generated phosphine-free Au(III) species have been proved to be the productive intermediates in the recently reported Au-catalyzed cross coupling reaction of aryl silanes with arenes. Interestingly, a catalytic reaction in the presence of Ph₃PAuCl gave no product conversion, thus highlighting the importance of the ancillary ligand in these transformations.
in marginal amounts (Figure 2b and Figure S6-7 in the SI). In contrast, the same reaction in the presence of PhI(OAc) favours the formation of the observed complex (equation 4 and Figures S20-21 in the SI). We set out to examine the reactivity of complexes PAuCl and methyl propiolate (5).

Once the species detected during the reaction had been identified, we decided to interrogate in detail both, the mechanism for the formation, as well as the reactivity of the Au(I)-acetylide complex 8. We monitored the formation of 8 from Ph3PAuCl, methyl propiolate (5) and NaHCO3 by both 1H and 31P NMR performing the reaction in CD2Cl2. Experimentally, the formation of complex 8 is not a favorable process, and even after prolonged heating, it could only be detected in marginal amounts (Figure 2b and Figure S6-7 in the SI). In contrast, the same reaction in the presence of Ph(OAc)2 revealed the presence of 8 after only 5 minutes (Figure 2c and Figures S8-9 in the SI), in line with the spectroscopic analysis of a catalytic reaction (Figure 2a). Interestingly, the reaction of Ph3PAuOAc with 5 proceeded quantitatively at room temperature in the absence of oxidant producing 8 and AcOH in only 10 minutes (Figure 2d). On the other hand, the reverse reaction, although not unfavorable, is not a favorable process. These observations suggested an additional and unexpected new role of the oxidant in the initial steps of the reaction: Ph(OAc)2 favors the formation of the observed complex 8 (Figure S10-13 in the SI).

The reactivity of the Au(I)-acetylide 8 was studied next. Gold acetylides have been proposed as productive reaction intermediates in different transformations including the formation of Au vinyldienes17 or the Au-catalyzed homo-18 and heterocoupling19 of alkynes. The reaction of 8 with Ph(OAc)2 in CD2Cl2 was monitored by 1H and 31P NMR. No conversion was observed up to 60 °C while only very low conversion into Ph3PAuOAc and Ph3PAuCl was detected even after prolonged heating at 90 °C (equation 2 and Figures S14-15 in the SI)19. These results indicate, that 8 is hardly oxidized with Ph(OAc)2 and also that the putative oxidation product Ph3PAu(CIC6F5)2(OAc)2 is, rather unstable under the reaction conditions undergoing rapid reductive elimination to give Ph3PAuOAc and 3-{(acetyloxy)-methyl) propionate (which decomposes in situ due to its highly labile nature).

In sharp contrast, the reaction of 8 in the presence of PhCl2 cleanly proceeded at room temperature to give cis-Ph3PAu(CIC6F5)(Cl)Cl (10), whose structure could be confirmed by X-ray diffraction analysis (equation 3). These results not only showcase the different oxidizing abilities of Ph(OAc)2 vs. PhCl2 but also the influence of the ligand transferred by the hypervalent iodine reagent on the stability of the corresponding Au(III) intermediates produced in the reaction mixture. When 8 and PhCl2 were stirred at higher temperature, reductive elimination on 10 occurred, furnishing Ph3PAuCl, which is oxidized in the presence of the remaining oxidant to Ph3PAuCl2. In this case, the by-product stemming from reductive elimination (i.e. 3-chloro-methyl propionate 111) could be clearly observed (equation 4 and Figures S20-21 in the SI).

Due to the labile nature of complex 9, we decided to seek an alternative model system to study the reactivity of the putative Au(III) intermediates produced during the aryl alkynylation reaction. Ph3PAuCF3 (12) was selected expecting that the electron deficient nature of the pentafluorophenyl ligand could mimic that of the propionate unit while offering a more stable platform for the isolation of gold(III) species. Reaction of Ph3PAuCF3 (12) with Ph(OAc)2 in a 1:1 mixture of hexafluorobenzene/benzene at 80 °C, delivered trans-Ph3PAu(C6F5)(OAc)2 (13) in 64% yield according to our previously reported procedure (equation 5).22

Reactivity of putative Au(III)-intermediates

We set out to examine the reactivity of complexes 10 and 13 towards the species present in the media during the standard aryl alkynylation reaction, namely: methyl propionate (5), Au(I)-acetylide complex 8 (and electron-rich arenes in a stoichiometric fashion. The results of this study have been summarized in Table 1. Interestingly, trans-Ph3PAu(C6F5)(OAc)2 (13) reacted with methyl propionate (5) at 25 °C to give methyl 3-(pentafluorophenyl)-prop-2-ynoate (14) in 68% yield together with Au(I)-acetylide complex 8 as a result of the double replacement of both acetato ligands with free alkene followed by reductive elimination (See Fig. S22-23 in the SI). The reaction of 13 with complex 8 was also illustrative, providing 14 in 62% yield together with Ph3PAuOAc. Since no Au(I)-acetylide complex 8 was detected at the end of the reaction, we have to assume that upon a first Au(I)/Au(III) transmetalation (which could also be described as a Au(III)/Au(III) ligand exchange reaction), Csp2-
Csp reductive elimination occurs fast, preventing a second ligand transfer between the different gold species (See Fig. S24-25 in the SI). Finally, the reactions of 13 with 1,3,5-trimethoxybenzene, 1,3-dimethoxytoluene 4 and N-methyl indole were also enlightening as they proceeded efficiently towards the corresponding cross-coupling products 15, 16 and 17 in 85, 74 and 85% yield, respectively. Table 1. Comparison of reactivity between Au(III)-bis-chloro vs. bis-acetato complexes.

| REACTIVITY | OAc vs. Cl |
|------------|------------|
| cis-ClAu(C≡CMe)(OAc)PAuCl | No Reaction<sup>a</sup> |
| cis-ClAu(C≡CMe)(OAc)PAuOAc | No Reaction<sup>a</sup> |
| cis-ClAu(C≡CMe)(OAc)PAuOAc | (85%)<sup>b</sup> |
| cis-ClAu(C≡CMe)(OAc)PAuOAc | (74%)<sup>b</sup> |

These experiments clearly suggest that the presence of free alkyne in the reaction mixture favors a productive reaction outcome and together with equation 2 highlight that neither PhI(OAc)<sub>2</sub> is an efficient oxidant for 8 nor the putative Ph<sub>3</sub>PdAu(C≡C-O2Me)(OAc)<sub>2</sub> (9) complex is a highly competent reaction intermediate. Additionally, the reactions shown in Figure 1b-d indicated that the oxidant is involved in the activation of the alkyne. We hypothesized that the formation of 8 could occur by ligand exchange on Ph<sub>3</sub>PdAuCl in the presence of PhI(OAc)<sub>2</sub> to form Ph<sub>3</sub>PdAuOAc which rapidly activates the alkyne 5 to form 8 and AcOH, that is then quenched by NaHCO<sub>3</sub> present in the reaction media (Figure 1d). This proposal is supported by recent experiments of Shi et al., showing the formation of R<sub>2</sub>PdAuOAc in presence of R<sub>2</sub>PdAuCl and PhI(OAc)<sub>2</sub> by MALDI-MS analysis. Thus, to gain a deeper insight into the specific nature of the individual steps involved in these transformations, DFT calculations and additional control experiments were carried out.

DFT Studies and Characterization of the Oxidizing Species

In line with the experimental observations summarized in Figure 2, calculations confirmed that formation of Au(I)-acetylide 8 from Ph<sub>3</sub>PdAuCl in the absence of oxidant is a highly unfavorable process even in the presence of base (19.1 kcal/mol, Figure 3a). The lack of reactivity observed for Ph<sub>3</sub>PdAuCl in the presence of PhI(OAc)<sub>2</sub> could also be confirmed. A potential Au(Cl)/I(OAc) exchange is also disfavored (+12.8 kcal/mol), and thus such an equilibrium would be strongly shifted towards the starting materials (Figure 3b). When alkyne is added into the system, the energies of these two equilibria remain unchanged. However, the trace amounts of Ph<sub>3</sub>PdAuOAc that could be produced rapidly react with the free alkyne present in the media to give Au(I)-acetylide complexes and acetic acid, which will be quenched with the base present in the reaction (Figure 3c and Figure 1d). The energy for this process decreases to +6.3 kcal/mol. Thus, the second equilibria will drive the first one towards the right, influenced by the presence of free alkyne. Furthermore, the in situ generated PhI(OAc)/Cl<sub>2</sub> intermediate presents a much lower activation energy towards the oxidation of Au(I) acetylide via TS<sub>3</sub> (+20.1 kcal/mol) compared to PhI(OAc)<sub>2</sub> via TS<sub>3</sub> (+29.2 kcal/mol) (Figure 3d).

Additional stoichiometric experiments with Au(I)-acetylide complex 8 were designed. When the reaction of 3,5-dimethoxytoluene (4) was run using Au(I)-acetylide 8 as stoichiometric alkynylating agent in the presence of PhI(OAc)<sub>2</sub> and NaHCO<sub>3</sub> only traces of the desired cross-coupling product 6 was detected (equation 7 and Fig. S32-33 in the SI). In contrast, when methyl propiolate (5) was incorporated in the reaction, aryalkyne product 6 was clearly observed after only one hour even if in low conversion (equation 8 and Fig. S34-35 in the SI). A catalytic version of this reaction using 5 mol% of 8 or Ph<sub>3</sub>PdAuOAc also afforded 6 although again, in a much less efficient manner compared to the standard conditions (equation 9 and Fig. S36-37 in the SI).

<sup>a</sup> Au(I)-acetylide 8 was also detected. <sup>b</sup>Ph<sub>3</sub>PdAuOAc was also detected. <sup>c</sup>Compound 16 is obtained as a 0.6:1 mixture of regioisomers. <sup>d</sup>Traces of alkynyl homocoupling product 18 were detected. <sup>e</sup>Ph<sub>3</sub>PdAuCl was also detected. See also ref. 16b.
stoichiometric experiments were subsequently designed to support the hypothesis of a Au(Cl)/I(OAc) ligand exchange triggered by the presence of free alkyne and the formation of a more reactive “non-symmetric” oxidant. In turn, 2-chloro-3,5-dimethoxytoluene could be detected, pointing towards in situ generated 21, which in this case is produced in abundant quantities in the reaction media, as chlorinating agent. In line with these results, in the absence of Cl available for ligand exchange, the performance of 8 or Ph3P=OAc as catalysts (equation 9) delivered the cross-coupling product in lower yield compared to the standard conditions.

The in situ kinetic studies of a reaction between 20, methyl propiolate (5) and Ph3P=OACl revealed the consumption of 20 and the simultaneous formation of a new product with a characteristic 19F signal at 107.5 ppm which was assigned to m-F-C6H4I(OAc)Cl (21) (Figure 4a-b). The oxidizing potential of 21 is higher than that of 20 as already revealed by the DFT calculations (Figure 3d) and thus the Au(II)-acylido complex 8 which has been generated in situ, can be slowly oxidized even at room temperature, thus preventing the accumulation of 21 in the reaction media. In the absence of other species, an OAc-alkyne ligand exchange reaction on the Au(III)-acylido intermediate (red path) or a transmetalation between the Au(I) and Au(III)-acylido species coexisting in the reaction media (blue path) could explain the formation of homocoupling product 18, which is produced in a comparable ratio to that in which 20 is consumed (Figure 4c). Additional experiments were carried out to support the proposed structure of compound 21: the reaction of m-F-C6H4I(Cl)2 with 1 equivalent of AgOAc delivered, after only 5 min, the same species observed in the 19F NMR spectrum, thus confirming the proposed composition of the “non-symmetric” oxidant (Figure 4d). (For these and additional control experiments, see section 3.8 in the SI).

Figure 4. Formation of “non-symmetric” Au(III) species by reaction of m-F-C6H4I(OAc)2 20 with Ph3P=OACl and methyl propiolate (5): a) Evolution of the temporal concentration of reactants, intermediates and product. b) 19F NMR traces of the reaction mixture. c) Rationalization of the observed species. d) Alternative synthesis and characterization of m-F-C6H4I(OAc)(Cl) (21).
Figure 5. Top: complete energy profile for the reaction between Ph₃PAuCl, alkyne (methyl alkynyl ketone), PhI(OAc)₂ and arene (1,3,5-trimethoxybenzene). Gibbs Free energy values in blue calculated with the M06 functional. Bottom: structures of transition states TS₁, TS₂ and TS₃ (left to right) highlighting the relevant distances.

Finally, DFT calculations were carried out to map the entire energy potential surface (Figure 5). The mixture of free alkyne, PhI(OAc)₂ and Ph₃PAuCl was taken as the ground state of energy (G = 0 kcal/mol), mimicking the initial experimental conditions. As detailed in Figure 5, the Cl/OAc anion exchange between the gold and the iodine centers through TS₁ (with Au-O₁ and I-Cl bond distances of 2.35 and 2.90 Å respectively) leads to a first high energy mixture, INT₁ (+12.8 kcal/mol), which is readily transformed into INT₂ (+6.3 kcal/mol) by deprotonation of the alkyne, alkynyl-gold complex formation and HOAc release via TS₂ (with bond distances: Au-C₁ = 2.34 Å, Au-O₁ = 2.46 Å and C₁-H = 1.23 Å). The oxidation of the alkynyl-gold complex by the active oxidant species PhI(OAc)(Cl) presents an affordable activation energy (+20.1 kcal/mol from INT₂ to TS₃), involving the rupture of the I-Cl bond (I-Cl = 3.10 Å, Au-Cl = 2.67 Å, Au-I = 3.32 Å and Au-C₁ = 2.0 Å). The alternative Au(I) to Au(III)oxidation involving the I-OAc bond of PhI(OAc)(Cl) is disfavoured by more than 8 kcal/mol with respect to TS₃ (Figure 3d). After the oxidation via INT₃, iodosubene is released to form a highly stable neutral intermediate INT₅A (-17.9 kcal/mol). The arene reacts then with INT₅A and the acetate ligand abstracts the proton to restore the aromaticity via TS₄A in an overall highly exergonic process to give INT₆ (-29.7 kcal/mol from INT₃), which is followed by a fast reductive elimination (the energy profile calculated for a dissociative interaction of the arene with INT₃ can be found in Figure S69 in the SI). Deuterium labelling experiments on
Mechanistic Proposal for the Au-catalyzed Alkynylation of Arenes. Structures of TS1, TS2, TS3 and TS5 stem from DFT calculations reported in Figure 5.

On the outset of the reaction, the formation of a Au(I)-acetylide complex F takes place. However, the reaction of methyl propiolate (E) and Ph3PAuCl in the presence of base to give acetylide complex F is not a favorable process (Figure 2b). In contrast, the same reaction in the presence of Ph(OAc)2 revealed the formation of F after only 5 minutes (Figure 2c), in line with the spectroscopic analysis of a catalytic reaction (Figure 2a). These results led us to discard a facile equilibrium between the Au pre-catalyst and the alkynyl while suggesting a new role for the oxidant in the initial steps of this transformation. Studies, including F-labeling experiments and DFT calculations support a mechanistic scenario involving multiple exchange between PhI(OAc)2, and also to that of the attack of the arene onto the alkynyl-gold(III) intermediate via TS4a. DFT calculations also confirmed the lability of aryl-aurate intermediate (INT4a), which rapidly evolves via reductive elimination towards the cross-coupling product regenerating the Ph3PAuCl catalyst.31,30

The data presented in previous sections enabled a more detailed mechanism for the Au-catalyzed alkynylation of arenes to be proposed based on a better understanding of both oxidant and catalyst speciation for a productive reaction outcome (Scheme 3).

The arene carried out in our seminal study7 showed no primary KIE, in line with the present DFT results in which arene auration is not turnover limiting. Ph3PAuCl is formed in the final stage, re-entering the cycle, which shows an overall reaction energy of -81 kcal/mol. Thus, the DFT results support the hypothesis of the transformation of gold(I)-chloride into gold(I)-acetate (INT1), and this into Au(I)-acetylide (INT2) through two up-hill equilibria. The activation energies for these processes are comparable to that of the subsequent oxidation step by the in situ generated Ph(OAc)(Cl) via transition state TS2, and also to that of the attack of the arene onto the alkynyl-gold(III) intermediate via TS4a. DFT calculations also confirmed the lability of aryloaurate intermediate (INT4a), which rapidly evolves via reductive elimination towards the cross-coupling product regenerating the Ph3PAuCl catalyst.31,30

Proposed Catalytic Cycle

The data presented in previous sections enabled a more detailed mechanism for the Au-catalyzed alkynylation of arenes to be proposed based on a better understanding of both oxidant and catalyst speciation for a productive reaction outcome (Scheme 3).
Experiments summarized in equations 2, 7, 8 and 9 clearly suggest that free alkyne favors a productive reaction outcome and also that PhI(OAc)₂ is not an efficient oxidant for 8 nor the putative Ph₃PAu(Cl–C=O–Me)(OAc) · 9 complex is a highly competent reaction intermediate. Still, alternative reaction pathways operating with PhI(OAc)₂ as oxidant cannot be completely ruled out (equation 9). Putative analogues of Au(III) complexes G (10 and 13 in Table 1) were used as mechanistic probes in stoichiometric experiments which revealed the crucial role of anionic ligands in the reaction outcome. Thus, acetato ligands on the Au(III) center can be rapidly exchanged in the presence of arenes whereas the corresponding chlorides remain unreacted. A competitive OAc/alkyne exchange in G to give G’ can occur although in a sufficiently slower rate to enable a productive cross coupling reaction rather than the undesired homocoupling of alkyne, which is sometimes observed as minor by-product in these transformations. Although a Au(I)/Au(III) transmetallation involving the chloride ligands towards the formation of a bis-alkynyl Au(III) intermediate cannot be completely ruled out,18,31 control experiments indicate that this process might be slow under the present reaction conditions (see Figure 4c and Figure S51-57 in the SI).

The proposed Au(Cl)⁻I(OAc) exchange in the first steps of the reaction produces a “non-symmetric” ArI(Cl)(OAc) oxidant responsible for reaction by-products stemming from the direct oxidation (i.e. chlorination) of the arene (< 5%) (section 4.2 in SI).32 Finally, the mechanism for catalyst decomposition has also been studied. Slow de-coordination of Ph₃P from the neutral starting complex Ph₃PAuCl or other phosphine-Au species involved in the reaction results in the formation of trace amounts of (Ph₃P)₂AuX (7) visible in the ³¹P NMR of the standard catalytic reaction media (Figure 2a). Control experiments revealed that these species are catalytically inactive and do not interfere with a productive reaction outcome (see section 4.3 in the SI).33

Conclusions

A detailed investigation of the gold-catalyzed alkylation of arenes including kinetic and stoichiometric experiments together with DFT calculations has provided an insightful perspective on the mechanism of this transformation. A ligand exchange involving alkyne, Au(I)-catalyst and oxidant is needed to form both, a Au(II) acetylide complex as well as a more reactive “non-symmetric” oxidant PhI(OAc)₂(Cl) responsible for the crucial Au(I)/Au(III) turnover. Both processes, i.e. the formation of Au(III)-acetylide and its oxidation, are connected through an equilibrium which evolves along the reaction progress. Reaction of the electron rich arenes with the in situ generated Au(III)-alkynyl intermediate occurs to produce a short-lived aryl-acetylnyl-Au(III) complex, which evolves by reductive elimination to produce the observed cross-coupling products and the Au(I) catalyst. The mechanisms of both, catalyst decomposition and competing side reactions, have also been unraveled. Few of the lessons learned in this study may also be applicable to other gold-catalyzed oxidative cross-couplings employing I(III) oxidants. Unexpectedly, a ligand exchange between the gold(I) precatalyst and the initial hypervalent iodine might be key to produce the suitable gold(III)-species to enable activation of the alkyne in the first place. Furthermore, the same process provides the appropriate oxidizing species, capable to produce reactive Au(III)-intermediates. This process is influenced by both, the nature of the ancillary ligand on gold as well as by the presence of other reaction partners which can shift this up-hill equilibria. Oxidation is also an energetically demanding process which translates into a Au(III)-intermediate, whose reactivity will be fine-tuned by the nature of the anionic ligands transferred by the oxidant: while acetato ligands favor activation of the arene and are easily displaced to give the cross-coupling products, chlorides are much less reactive and thus stabilize these species favoring transmetallation processes. We believe this mechanistic study supporting Au(I)/Au(III) redox catalytic cycles provides novel insights, useful not only for the development of new gold catalyzed oxidative transformations but also for the improvement and fine-tuning of already available ones.

Conflicts of interest

There are no conflicts to declare.

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