



Cite this: *Chem. Sci.*, 2019, 10, 8411

All publication charges for this article have been paid for by the Royal Society of Chemistry

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

Manuel Hofer,^a Teresa de Haro,^a Enrique Gómez-Bengoia,^b Alexandre Genoux^a and Cristina Nevado^{*,a}

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 an Au(I)-acetylide complex and 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 in the reactivity of the key Au(III) intermediates.

Received 15th May 2019

Accepted 9th July 2019

DOI: 10.1039/c9sc02372k

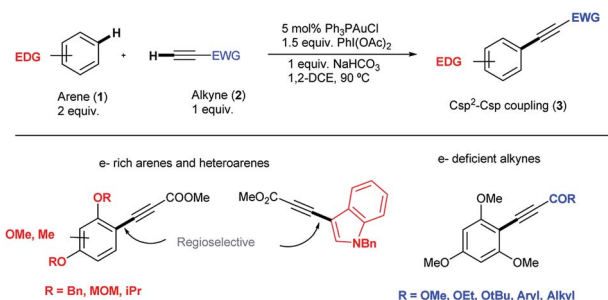
rsc.li/chemical-science

Introduction

Aryl alkynes have found widespread use as building blocks in the synthesis of numerous natural products, bioactive molecules and organic materials.¹ 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.² 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,³ the direct Csp²–H alkynylation of arenes has been much less explored. Few examples though have shown the viability of this strategy.⁴ In 2010, the Cu-catalyzed direct alkynylation of electron deficient polyfluoroarenes with terminal alkynes using O₂ as the oxidant was reported by Su *et al.*⁵ 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 alkynylodonium species as an electrophilic source of acetylenic

moieties in the presence of catalytic amounts of late transition metals as demonstrated by Waser *et al.*⁶ In this context, our group reported an oxidative alkynylation of arenes *via* Au-catalyzed C–H functionalization of both Csp- and Csp²–H bonds (eqn (1) and Scheme 1).⁷ 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 the stoichiometric oxidant was found to be effective in producing new Csp²–Csp bonds.⁸ A stoichiometric version of this transformation had been already described by Fuchita and co-workers back in 2001.⁹

In the catalytic version, a hypervalent iodine reagent¹⁰ was selected as the oxidant on the basis of significant evidence that these species could promote Pd(II)/Pd(IV) catalytic cycles.¹¹ We



Scheme 1 Au-catalyzed alkynylation of arenes.

^aDepartment of Chemistry, University of Zürich, Winterthurerstrasse 190, Zürich, CH-8057, Switzerland. E-mail: cristina.nevado@chem.uzh.ch

^bDepartamento de Química Orgánica I, Universidad del País Vasco, Apdo 1072, CP-20080 Donostia-San Sebastián, Spain

† Electronic supplementary information (ESI) available. CCDC 1008765. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc02372k



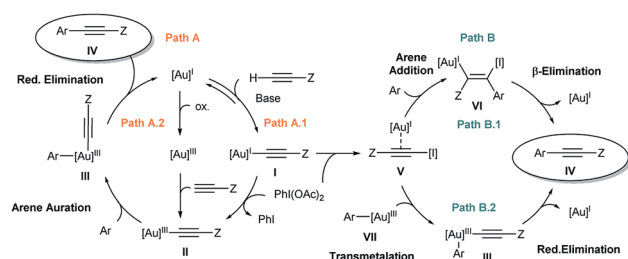
thus anticipated that a Au(I)/Au(III) catalytic turnover could be implemented under the reaction conditions. Furthermore, the ability of Au(III) species to trigger Csp²-H activation in electron rich arenes is also well established.^{9,12} Although Au(I)/Au(III)-catalyzed reactions have recently emerged as powerful tools for C-C cross couplings,¹³ with few notable exceptions,¹⁴ the mechanistic understanding of these processes is still limited and the characterization of putative intermediates is scarce. We report herein a detailed investigation aiming to elucidate the factors governing both reactivity and selectivity in these transformations.

In our previous work,⁷ the mechanistic rationale involved: (i) an equilibrium between the free alkyne and the Au catalyst with the aid of a base to form a Au(I)-acetylide complex (**I**); (ii) oxidation of **I** with PhI(OAc)₂ to form Au(III) species **II**; (iii) arene auration to produce intermediate **III** which evolves *via* reductive elimination (iv) yielding product **IV** (Scheme 2, path A.1). Alternatively, in line with Waser's reports on the stoichiometric use of alkynylidonium salts,⁶ a ligand exchange between PhI(OAc)₂ and Au(I)-acetylide (**I**) to give an alkynylidonium intermediate (**V**) could also be proposed. Arene addition to give **VI** followed by β-Au elimination would then furnish product **IV** as shown in path B.1 of Scheme 2. Alternatively, transmetalation between alkynylidonium salt **V** and putative aryl-Au(III) species (**VII**) produced *in situ* within the oxidative reaction media¹² could also deliver intermediate **III**, which would yield the observed products after reductive elimination as shown in Scheme 2, path B.2.

Our preliminary study left open 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.⁷

Results and discussion

Initial experiments¹⁵ to investigate the feasibility of pathways B.1 and B.2 focused on alkynylidonium salts (**V**) in order to reveal their potential role as intermediates in these transformations.



Scheme 2 Plausible mechanisms for Au-catalyzed alkylation of arenes.

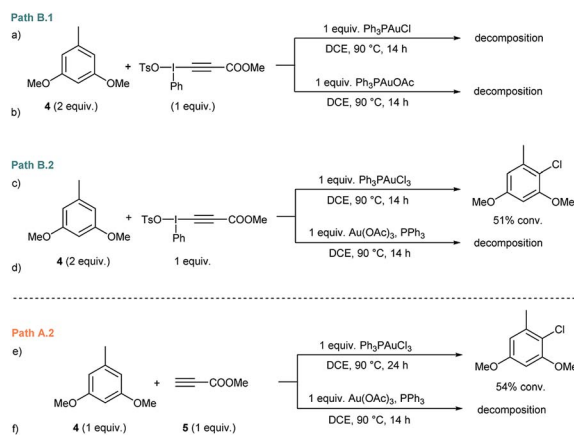


Fig. 1 (a–d) Stoichiometric experiments involving alkynylidonium species (paths B.1 and B.2 in Scheme 2). (e and f) Stoichiometric experiments regarding path A.2.

Treatment of methyl 3-(phenyl(tosyloxy)-λ³-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 alkynylidonium salt was detected (Fig. 1a and b). Identical experiments in the presence of gold(III) complexes like Ph₃PAuCl₃ or Au(OAc)₃/PPh₃ showed a similar outcome (Fig. 1c and d). Interestingly, in the case of Ph₃PAuCl₃ formation of 2-chloro-1,5-dimethoxy-3-methylbenzene as the by-product could be observed.^{12a} These control experiments (Section 2 in the ESI†) led us to rule out pathways B.1 and B.2 and the participation of alkynylidonium species **V** as intermediates in these transformations.

Experiments to investigate pathway A.2 involved the participation of the alkyne in the presence of gold(III) species. However, stoichiometric experiments with 3,5-dimethoxytoluene (**4**), methyl propiolate (**5**) and Ph₃PAuCl₃ or Au(OAc)₃/PPh₃ at 90 °C showed the formation of the arylchloride in the case of Ph₃PAuCl₃ but no participation of the alkyne (Fig. 1e and f). To explore the direct oxidation of the initial catalyst, Ph₃PAuCl was treated with an 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 (Fig. S2 and S3 in the ESI†). These experiments suggest that the neutral Ph₃PAuCl complex used as the catalyst is scarcely oxidized by PhI(OAc)₂ under the reaction conditions, in contrast to previous results obtained for PhICl₂ which furnished Ph₃PAuCl₃ in 96% yield even at room temperature.¹⁶ *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.^{14a,b} However, the results described herein clearly indicate that the present alkylation reaction proceeds, at least at 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 Ph_3PAuCl , $[(\text{Ph}_3\text{P})_2\text{Au}]\text{Cl}$ (7) and a $\text{Ph}_3\text{PAu}(\text{C}\equiv\text{C}-\text{CO}_2\text{Me})$ complex (8) (Fig. 2a, S4 and S5 in the ESI†).

Complex 8 appears already after the first minutes of the reaction and it disappears towards the end whereas Ph_3PAuCl and 7 are present after the starting materials have been completely consumed. Ph_3PO 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 $\text{PhI}(\text{OAc})_2$ 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.^{14c} Interestingly, a catalytic reaction in the presence of IPrAuCl gave no product conversion, thus highlighting the importance of the ancillary ligand in these transformations.

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 8. We monitored the formation of 8 from Ph_3PAuCl , methyl propiolate (5) and NaHCO_3 by both ^1H and ^{31}P NMR performing the reaction in CD_2Cl_2 . Experimentally, the formation of complex 8 is not a favorable process, and even after prolonged heating, it could only be detected in marginal amounts (Fig. 2b, S6 and S7 in the ESI†). In contrast, the same reaction in the presence of $\text{PhI}(\text{OAc})_2$ revealed the presence of 8 after only 5 minutes (Fig. 2c, S8 and S9 in the ESI†), in line with the spectroscopic analysis of a catalytic reaction (Fig. 2a). Interestingly, the reaction of Ph_3PAuOAc with 5 proceeded quantitatively at room temperature in the absence of oxidant producing 8 and AcOH in only 10 minutes (Fig. 2d). On the other hand, the reverse reaction, although not unfeasible, is not a favorable process. These observations suggested an additional

and unexpected new role of the oxidant in the initial steps of the reaction: $\text{PhI}(\text{OAc})_2$ favors the formation of the observed complex 8 (Fig. S10–S13 in the ESI†).

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 vinylidenes¹⁷ or the Au-catalyzed homo-¹⁸ and heterocoupling¹⁹ of alkynes. The reaction of 8 with $\text{PhI}(\text{OAc})_2$ in CD_2Cl_2 was monitored by ^1H and ^{31}P NMR. Indeed, no conversion was observed up to 60 °C while only very low conversion into Ph_3PAuOAc and Ph_3PAuCl was detected even after prolonged heating at 90 °C (eqn (2), Fig. S14 and S15 in the ESI†).²⁰ These results indicate that 8 is hardly oxidized with $\text{PhI}(\text{OAc})_2$ and also that the putative oxidation product $\text{Ph}_3\text{PAu}(\text{C}\equiv\text{C}-\text{CO}_2\text{Me})(\text{OAc})_2$ 9 is rather unstable under the reaction conditions undergoing rapid reductive elimination to give Ph_3PAuOAc and 3-(acetyloxy)-methyl propiolate (which decomposes *in situ* due to its highly labile nature).

In sharp contrast, the reaction of 8 in the presence of PhICl_2 cleanly proceeded at room temperature to give *cis*- $\text{Ph}_3\text{PAu}(\text{C}\equiv\text{C}-\text{CO}_2\text{Me})(\text{Cl})_2$ keep "cis- $\text{Ph}_3\text{PAu}(\text{CC}-\text{CO}_2\text{Me})(\text{Cl})_2$ (10)" in single line(10), whose structure could be confirmed by X-ray diffraction analysis (eqn (3)). These results not only showcase the different oxidizing abilities of $\text{PhI}(\text{OAc})_2$ vs. PhICl_2 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 PhICl_2 were stirred at higher temperature, reductive elimination on 10 occurred, furnishing Ph_3PAuCl , which is oxidized in the presence of the remaining oxidant to $\text{Ph}_3\text{PAuCl}_3$. In this case, the by-product stemming from reductive elimination (*i.e.* 3-chloro-methyl propiolate 11²¹) could be clearly observed (eqn (4), Fig. S20 and S21 in the ESI†).

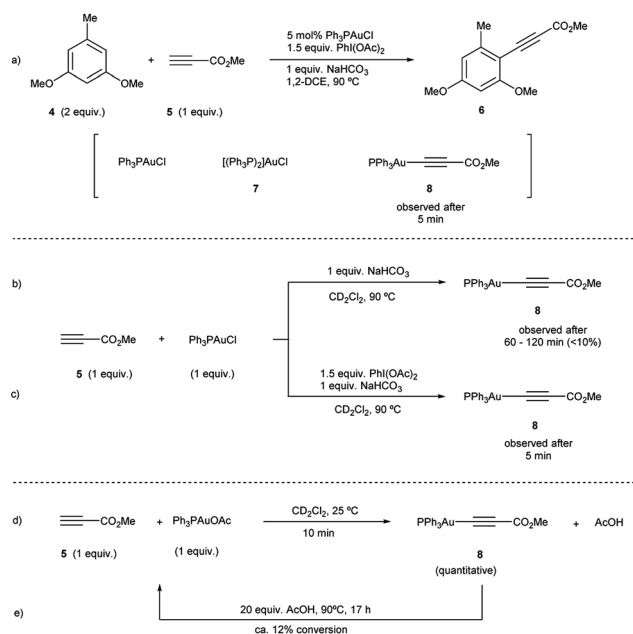
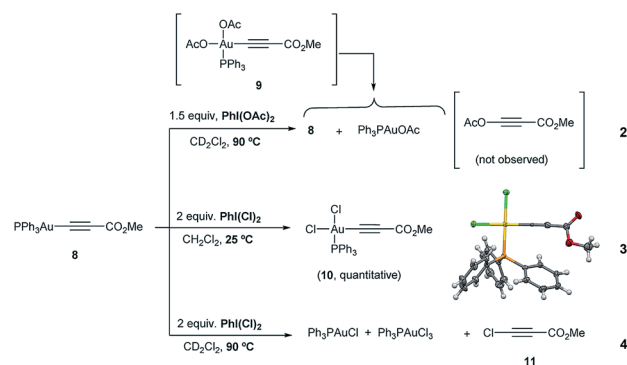
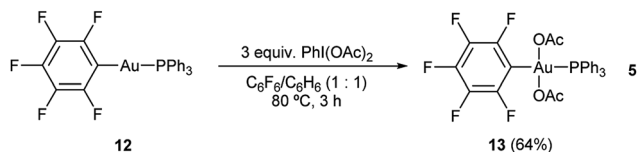


Fig. 2 (a) Standard catalytic reaction. (b and c) Experiments towards the formation of Au(I)-acetylide 8 from Ph_3PAuCl and alkyne 5 in the absence or presence of $\text{PhI}(\text{OAc})_2$, respectively. (d and e) Reactivity of Ph_3PAuOAc towards methyl propiolate (5).



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. $\text{Ph}_3\text{PAu}(\text{C}_6\text{F}_5)$ (12) was selected expecting that the electron deficient nature of the pentafluorophenyl ligand could mimic that of the propiolate unit while offering a more stable platform for the isolation of gold(III) species. Reaction of $\text{Ph}_3\text{PAu}(\text{C}_6\text{F}_5)$ (12) with $\text{PhI}(\text{OAc})_2$ in a 1 : 1 mixture of hexafluorobenzene/benzene at 80 °C delivered *trans*- $\text{Ph}_3\text{PAu}(\text{C}_6\text{F}_5)(\text{OAc})_2$ (13) in 64% yield according to our previously reported procedure (eqn (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 propiolate (**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 propiolate (**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 alkyne followed by reductive elimination (see Fig. S22 and S23 in the ESI†). 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(I)/Au(III) ligand exchange reaction), Csp²–Csp reductive elimination occurs fast, preventing a second ligand transfer between the different gold species (see Fig. S24 and S25 in the ESI†). 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.^{16b,23}

Table 1 Comparison of reactivity between Au(III)-bis-chloro vs. bis-acetato complexes

Reactivity OAc vs. Cl		
		No Reaction ^d
		No reaction ^f

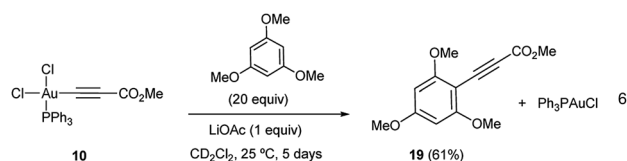
^a Au(I)-acetylide **8** was also detected. ^b Ph₃PAuOAc was also detected.

^c Compound **16** is obtained as a 0.6 : 1 mixture of regioisomers.

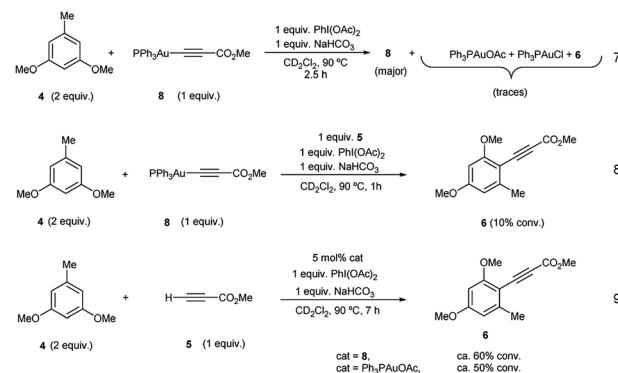
^d Traces of alkyne homocoupling product **18** were detected.

^e Ph₃PAuCl was also detected. ^f See also ref. 16b.

The reactivity pattern observed for *cis*-dichloro(methoxycarbonyl)ethynyl (triphenylphosphine)-gold(III) (**10**) turned out to be completely different as shown on the right column of Table 1. In contrast to **13**, complex **10** did not react with methyl propiolate (**5**) (Fig. S26 and S27 in the ESI†) although it underwent transmetalation with Au(I)-acetylide complex **8** even at –25 °C to give alkyne homocoupling product **18** (ref. 24) and Ph₃PAuCl. As in the previous case, only one Cl/alkyne ligand exchange took place (Fig. S28 and S29 in the ESI†). Also in contrast to **13**, *cis*-Ph₃PAu(C≡C–CO₂Me)(Cl)₂ (**10**) proved to be completely unreactive towards electron-rich aromatic nucleophiles even after prolonged heating at 130 °C (Fig. S30 and S31 in the ESI†).^{16b,25} The experiments summarized in Table 1 showcase the strong differences in reactivity for diacetato-Au(III) vs. dichloro-Au(III) complexes²⁶ and highlight the importance of the oxidant of choice, *i.e.* the ligand that ultimately the oxidant transfers onto the metal center, for a productive reaction outcome. In line with this hypothesis, replacement of the chloro ligands in **10** by reaction with 1 equivalent of LiOAc in the presence of 1,3,5-trimethoxybenzene in excess resulted in the clean formation of Ph₃PAuCl and alkynylation product **19** in 61% yield (eqn (6)).



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 the stoichiometric alkynyating agent in the presence of PhI(OAc)₂ and NaHCO₃ only traces of the desired cross-coupling product **6** were detected (eqn (7), Fig. S32 and S33 in the ESI†). In contrast, when methyl propiolate (**5**) was incorporated into the reaction, arylalkyne product **6** was clearly observed after only one hour even if in low conversion (eqn (8), Fig. S34 and S35 in the ESI†). A catalytic version of this reaction using 5 mol% of **8** or Ph₃PAuOAc also afforded **6** although again, in a much less efficient manner compared to the standard conditions (eqn (9), Fig. S36 and S37 in the ESI†).



These experiments clearly suggest that the presence of free alkyne in the reaction mixture favors a productive reaction



outcome and together with eqn (2) highlight that $\text{PhI}(\text{OAc})_2$ is not an efficient oxidant for **8** and the putative $\text{Ph}_3\text{PAu}(\text{C}\equiv\text{C}-\text{CO}_2\text{Me})(\text{OAc})_2$ (**9**) complex is not a highly competent reaction intermediate. Additionally, the reactions shown in Fig. 2b–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_3PAuCl in the presence of $\text{PhI}(\text{OAc})_2$ to form Ph_3PAuOAc which rapidly activates the alkyne **5** to form **8** and AcOH , which is then quenched by NaHCO_3 present in the reaction media (Fig. 2d). This proposal is supported by recent experiments of Shi *et al.*, showing the formation of R_3PAuOAc in the presence of R_3PAuCl and $\text{PhI}(\text{OAc})_2$ by MALDI-MS analysis.²⁷ 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 Fig. 2, calculations confirmed that formation of $\text{Au}(\text{I})$ -acetylide **8** from Ph_3PAuCl in the absence of oxidant is a highly unfavorable process even in the presence of base (+19.1 kcal mol^{−1}, Fig. 3a). The lack of reactivity observed for Ph_3PAuCl in the presence of $\text{PhI}(\text{OAc})_2$ could also be confirmed. A potential $\text{Au}(\text{Cl})/\text{I}(\text{OAc})$ exchange is also disfavored (+12.8 kcal mol^{−1}), and thus such an equilibrium would be strongly shifted towards the starting materials (Fig. 3b). When alkyne is added into the system, the energies of these two equilibria remain unchanged. However, the trace amounts of Ph_3PAuOAc that could be produced rapidly react with the free alkyne present in the media to give $\text{Au}(\text{I})$ -acetylide complexes and acetic acid, which will be quenched with the base present in the reaction (Fig. 3c and 2d). The energy for this process decreases to +6.3 kcal mol^{−1}. Thus, the second equilibria will drive the first one towards the right, influenced by the presence of free alkyne. Furthermore, the *in situ* generated $\text{PhI}(\text{OAc})(\text{Cl})$ intermediate presents a much lower activation energy towards the oxidation of $\text{Au}(\text{I})$ acetylide *via* TS_3 (+20.1 kcal mol^{−1}) compared to $\text{PhI}(\text{OAc})_2$ *via* TS_3' (+29.2 kcal mol^{−1}) (Fig. 3d).

Stoichiometric experiments were subsequently designed to support the hypothesis of a $\text{Au}(\text{Cl})/\text{I}(\text{OAc})$ ligand exchange triggered by the presence of free alkyne and the formation of a more reactive “non-symmetrical” oxidant. In an attempt to detect such species by highly sensitive ¹⁹F NMR spectroscopy, a fluorine-containing iodonium diacetate, namely *m*-F- $\text{C}_6\text{H}_4\text{I}(\text{OAc})_2$ (**20**), was synthesized.²⁸

The *in situ* kinetic studies of a reaction between **20**, methyl propiolate (**5**) and Ph_3PAuCl 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- $\text{C}_6\text{H}_4\text{I}(\text{OAc})(\text{Cl})$ (**21**) (Fig. 4a and b). The oxidizing potential of **21** is higher than that of **20** as already revealed by the DFT calculations (Fig. 3d) and thus the $\text{Au}(\text{I})$ -acetylide 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 $\text{Au}(\text{III})$ -acetylide intermediate

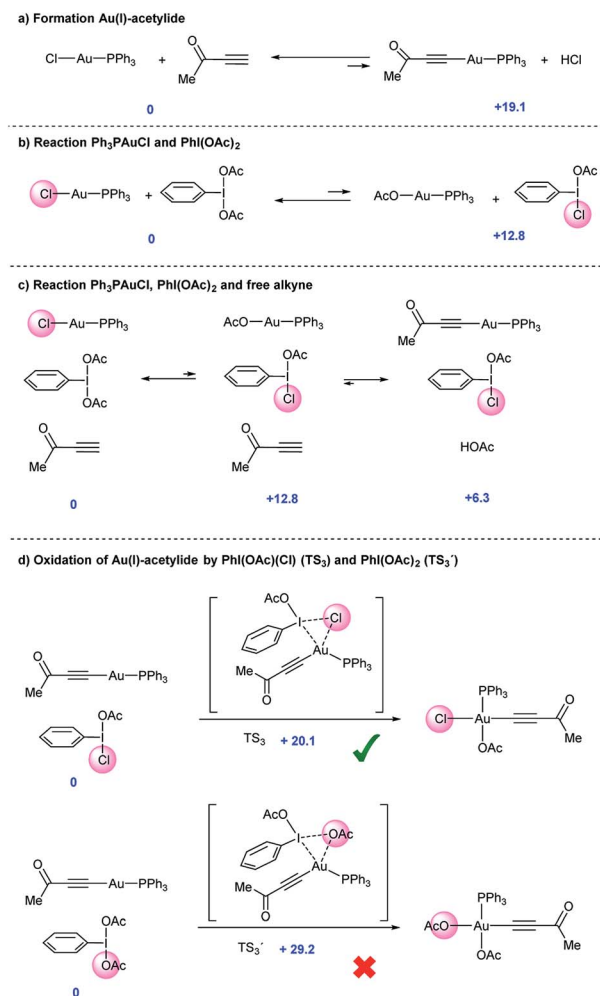


Fig. 3 (a–d) Computed Gibbs free energy values (kcal mol^{−1}) for the potential reaction between Ph_3PAuCl , alkyne (methyl alkynyl ketone) and hypervalent iodine reagents calculated with the M06 functional.

(red path) or a transmetalation between the $\text{Au}(\text{I})$ and $\text{Au}(\text{III})$ -acetylide 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 (Fig. 4c). Additional experiments were carried out to support the proposed structure of compound **21**: the reaction of *m*-F- $\text{C}_6\text{H}_4\text{I}(\text{Cl})_2$ 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 (Fig. 4d) (for these and additional control experiments, see Section 3.8 in the ESI†).

To confirm the ability of chloride transfer from Ph_3PAuCl to $\text{PhI}(\text{OAc})_2$, the standard cross-coupling reaction was performed in the presence of 1 equivalent of (*n*-Bu)₄NCl (see Section 3.9 in the ESI†). As expected, the initial excess of chloride in the reaction mixture inhibited the formation of the desired cross-coupling product. 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 the chlorinating agent. In line with these results, in the



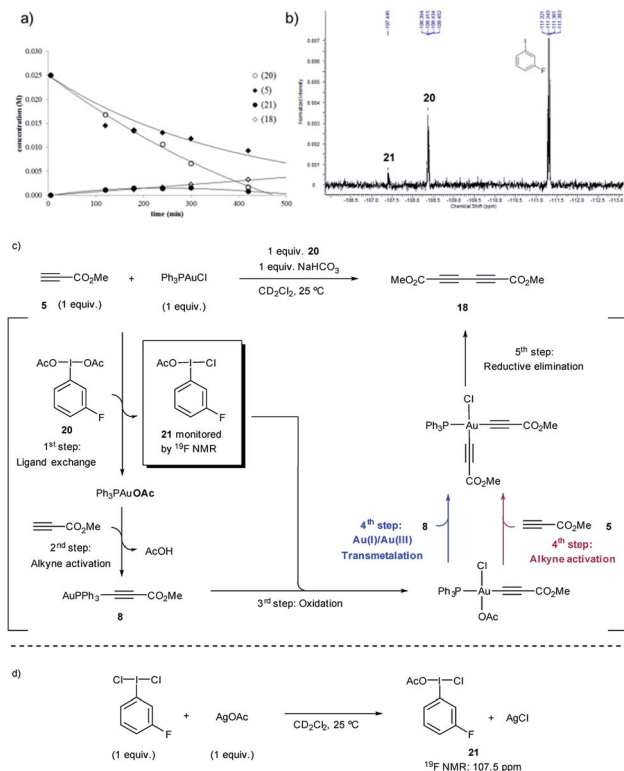


Fig. 4 Formation of "non-symmetric" I(III) species by reaction of *m*-F-C₆H₄I(OAc)₂ **20** with Ph₃PAuCl and methyl propiolate (**5**): (a) Evolution of the temporal concentration of reactants, intermediates and product. (b) ¹⁹F NMR traces of the reaction mixture. (c) Rationalization of the observed species. (d) Alternative synthesis and characterization of *m*-F-C₆H₄I(OAc)(Cl) (**21**).

absence of chloride available for ligand exchange, the performance of **8** or Ph₃PAuOAc as catalysts (eqn (9)) delivered the cross-coupling product in lower yield compared to the standard conditions.

Finally, DFT calculations were carried out to map the entire energy potential surface (Fig. 5). The mixture of free alkyne, PhI(OAc)₂ and Ph₃PAuCl was taken as the ground state of energy (*G* = 0 kcal mol^{−1}), mimicking the initial experimental conditions. As detailed in Fig. 5, the Cl/OAc anion exchange between the gold and the iodine center through **TS**₁ (with Au–O₁ and I–Cl bond distances of 2.35 and 2.90 Å respectively) leads to a first high energy mixture, **INT**₁ (+12.8 kcal mol^{−1}), which is readily transformed into **INT**₂ (+6.3 kcal mol^{−1}) by deprotonation of the alkyne, alkynyl-gold complex formation and HOAc release *via* **TS**₂ (with bond distances: Au–C₁ = 2.34 Å, Au–O₁ = 2.46 Å and C₁–H = 1.23 Å).²⁹ The oxidation of the alkynyl-gold complex by the active oxidant species PhI(OAc)(Cl) presents an affordable activation energy (+20.1 kcal mol^{−1} from **INT**₂ to **TS**₃), 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^{−1} with respect to **TS**₃ (Fig. 3d). After the oxidation *via* **INT**₃, iodobenzene is released to form a highly stable neutral intermediate **INT**_{5A} (−17.9 kcal mol^{−1}).

The arene reacts then with **INT**_{5A} and the acetate ligand abstracts the proton to restore the aromaticity *via* **TS**_{4A} in an overall highly exergonic process to give **INT**₆ (−29.7 kcal mol^{−1} from **INT**₃), which is followed by a fast reductive elimination (the energy profile calculated for a dissociative interaction of the arene with **INT**₃ can be found in Fig. S69 in the ESI†).¹⁵ Deuterium labelling experiments on 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^{−1}. Thus, the DFT calculations support the hypothesis of the transformation of gold(I)-chloride into gold(I)-acetate (**INT**₁), and this into Au(I)-acetylide (**INT**₂) 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 PhI(OAc)(Cl) *via* transition state **TS**₃ and also to that of the attack of the arene onto the alkynyl-gold(III) intermediate *via* **TS**_{4A}. DFT calculations also confirmed the lability of the arylaurate intermediate (**INT**₆), which rapidly evolves *via* reductive elimination towards the cross-coupling product regenerating the Ph₃PAuCl catalyst.^{23,30}

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).

At the outset of the reaction, the formation of an Au(I)-acetylide complex **F** takes place. However, the reaction of methyl propiolate (**E**) and Ph₃PAuCl in the presence of a base to give acetylide complex **F** is not a favorable process (Fig. 2b). In contrast, the same reaction in the presence of PhI(OAc)₂ revealed the formation of **F** after only 5 minutes (Fig. 2c), in line with the spectroscopic analysis of a catalytic reaction (Fig. 2a). These results led us to discard a facile equilibrium between the Au pre-catalyst and the alkyne 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 equilibria between the alkyne, oxidant and gold. Initially, a ligand exchange between Ph₃PAuCl and PhI(OAc)₂ delivers Ph₃PAuOAc and a non-symmetric oxidant, PhI(OAc)(Cl). As shown in Fig. 2d, 3a and b, free alkyne reacts with the trace amounts of Ph₃PAuOAc to give Au(I)-acetylide complex **F** and acetic acid, which is quenched in the presence of NaHCO₃. Experimentally, the formation of a non-symmetric hypervalent iodine *m*-F-PhI(OAc)(Cl) (**21**) could also be monitored by ¹⁹F NMR (Fig. 4). This new oxidant formed *in situ* presents a lower activation energy towards the oxidation of **F** into Au(III)-acetylide complex **G** compared to PhI(OAc)₂ (ΔΔ*G*[‡] *ca.* 9 kcal mol^{−1}, Fig. 3d). Experiments summarized in eqn (2) and (7)–(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 is the putative Ph₃PAu(C≡C–CO₂Me)(OAc)₂ (**9**) complex a highly competent reaction intermediate. Still, alternative reaction



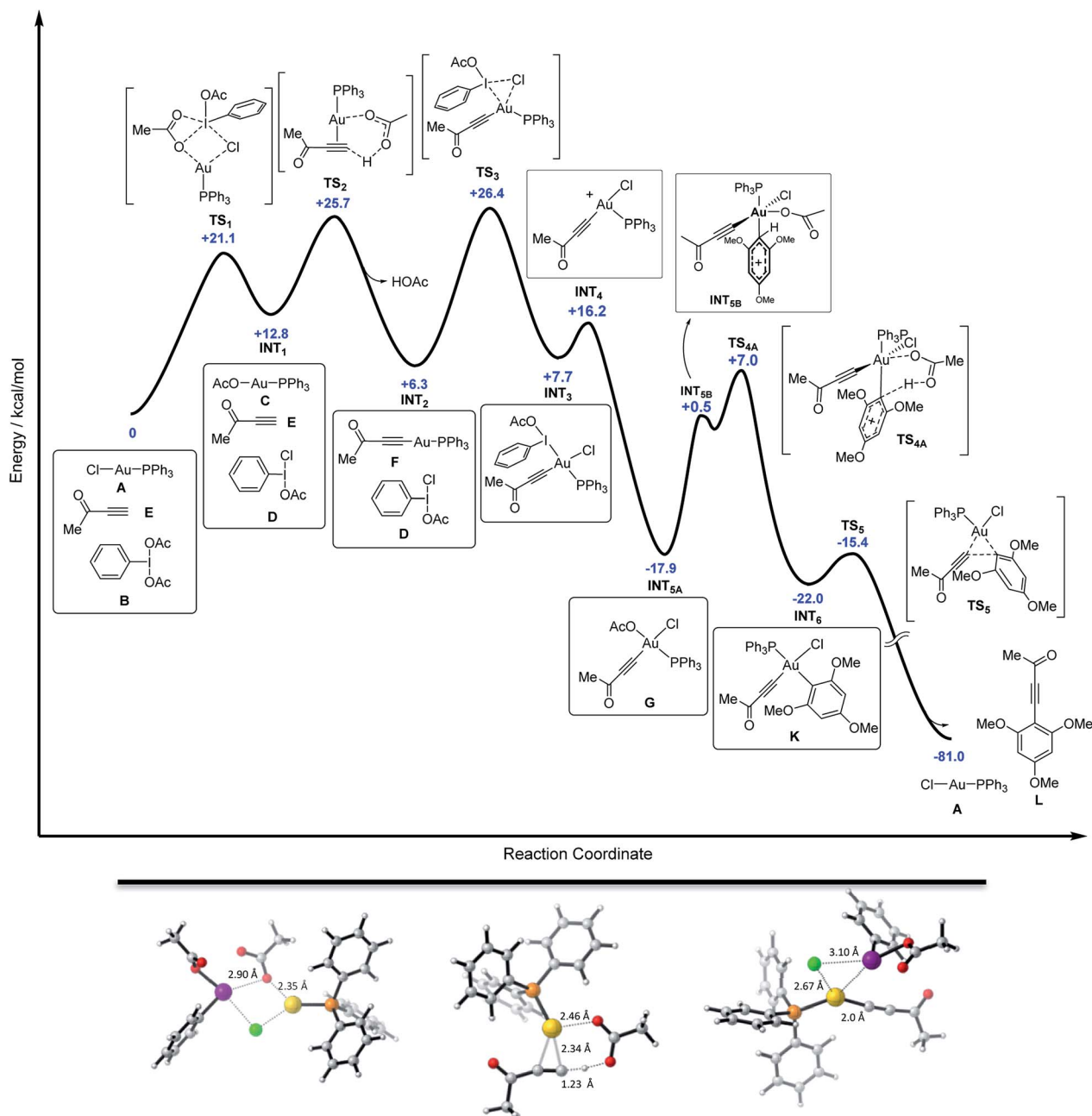


Fig. 5 Top: complete energy profile for the reaction between Ph_3PAuCl , alkyne (methyl alkynyl ketone), $\text{PhI}(\text{OAc})_2$ and arene (1,3,5-trimethoxybenzene). Gibbs free energy values in blue calculated with the M06 functional. Bottom: structures of transition states TS_1 , TS_2 and TS_3 (left to right) highlighting the relevant distances.

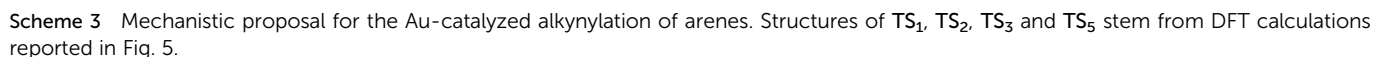
pathways operating with $\text{PhI}(\text{OAc})_2$ as the oxidant cannot be completely ruled out (eqn (9)). Putative analogues of $\text{Au}(\text{III})$ complexes **G** (**10** and **13** in Table 1) were used as mechanistic probes in stoichiometric experiments which revealed the crucial role of anionic ligands in the reaction outcome. Thus, acetato ligands on the $\text{Au}(\text{III})$ 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 a minor by-product in these transformations. Although a $\text{Au}(\text{I})/\text{Au}(\text{III})$ transmetalation involving the chloride ligands towards the formation of a bis-alkynyl $\text{Au}(\text{III})$ intermediate cannot be completely ruled out,^{18,31} control experiments indicate that this process might be slow under the present reaction conditions (see Fig. 4c and S51–S57 in the ESI†).

The proposed $\text{Au}(\text{Cl})\text{I}(\text{OAc})$ exchange in the first steps of the reaction produces a “non-symmetric” $\text{ArI}(\text{Cl})(\text{OAc})$ oxidant





Conclusions

needed to form both a Au(I)-acetylide complex and a more reactive “non-symmetric” oxidant PhI(OAc)(Cl) responsible for the crucial Au(I)/Au(III) turnover. Both processes, *i.e.* the formation of Au(I)-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-alkynyl-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.

A 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) pre-catalyst and the initial hypervalent iodine might be the key to produce the suitable gold(I)-species to enable activation of the alkyne in the first place. Furthermore, the same process provides the appropriate oxidizing species,

capable of producing reactive Au(III)-intermediates. This process is influenced by both the nature of the ancillary ligand on gold and by the presence of other reaction partners which can shift this uphill 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 transmetalation processes. We believe that 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.

Acknowledgements

We thank the European Research Council (ERC Starting grant agreement no. 307948) and the Swiss National Science Foundation (SNF 200020_146853) for financial support and the SGI/IZO-SGIker UPV/EHU and Schrödinger (UZH) for allocation of computational resources. We thank Dr A. Linden for the X-ray crystal structure determination of **10** (CCDC-1008765).†

Notes and references

- (a) P. J. Garatt, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 3, p. 271; (b) *Acetylene Chemistry: Chemistry, Biology and Material Science*, ed. F. Diederich, P. J. Stang and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005.
- (a) *Metal-Catalyzed Cross-Coupling Reactions*, ed. A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2nd edn, 2004, vol. 1, p. 2; (b) R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922.
- For recent reviews in C–H arylation, see: (a) *Modern Arylation Methods*, ed. L. Ackermann, Wiley-VCH, Weinheim, Germany, 2009, p. 311; (b) R. Giri, B.-F. Shi, K.-M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (c) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (d) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20–40.
- (a) F. Besselièvre and S. Piguel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9553–9556; (b) Z. Shao and F. Peng, *Angew. Chem., Int. Ed.*, 2010, **49**, 9566–9568; (c) A. S. Dudnik and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2010, **49**, 2096–2098; (d) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 2358–2361; (e) B. Pacheco Berciano, S. Lebrequier, F. Besselièvre and S. Piguel, *Org. Lett.*, 2010, **12**, 4038–4041; (f) C. Theunissen and G. Evano, *Org. Lett.*, 2014, **16**, 4488–4491.
- Y. Wei, H. Zhao, J. Kan, W. Su and M. Hong, *J. Am. Chem. Soc.*, 2010, **132**, 2522–2523.
- (a) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem., Int. Ed.*, 2009, **48**, 9346–9349; (b) J. P. Brand and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 7304–7307; (c) J. P. Brand, C. Chevalley and J. Waser, *Beilstein J. Org. Chem.*, 2011, **7**, 565–569; (d) J. P. Brand, C. Chevalley, R. Scopelliti and J. Waser, *Chem.-Eur. J.*, 2012, **18**, 5655–5666; (e) Y. Li, J. P. Brand and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 6743–6747; (f) Y. Li and J. Waser, *Beilstein J. Org. Chem.*, 2013, **9**, 1763; (g) J. P. Brand, Y. Li and J. Waser, *Isr. J. Chem.*, 2013, **53**, 901–910.
- T. de Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512–1513.
- For a Au-catalyzed tandem allenolate cyclization/alkynylation protocol with Selectfluor as the oxidant, see: M. N. Hopkinson, J. E. Ross, G. T. Giuffredi, A. D. Gee and V. Gouverneur, *Org. Lett.*, 2010, **12**, 4904–4907.
- Y. Fuchita, Y. Utsonomiya and M. Yasutake, *J. Chem. Soc., Dalton Trans.*, 2001, 2330–2334.
- (a) V. V. Zhdankin, *ARKIVOC*, 2009, 1; (b) R. M. Moriarty, *Org. Chem.*, 2005, **70**, 2893–2903; (c) J. P. Brand, D. Fernandez Gonzalez, S. Nicolai and J. Waser, *Chem. Commun.*, 2011, **47**, 102–115. For a seminal example of Au(I)/Au(III) involving hypervalent iodine reagents, see: A. Kar, N. Mangu, H. M. Kaiser, M. Beller and M. K. Tse, *Chem. Commun.*, 2008, 386–388.
- (a) N. R. Deprez and M. Sanford, *Inorg. Chem.*, 2007, **46**, 1924–1935; (b) P. A. Sibbald and F. E. Michael, *Org. Lett.*, 2009, **11**, 1147–1149; (c) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, P. Tang, W. A. Goddard III and T. Ritter, *J. Am. Chem. Soc.*, 2010, **132**, 3793–3801; (d) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824–889.
- (a) M. S. Kharasch and H. S. Isbell, *J. Am. Chem. Soc.*, 1931, **53**, 3053–3059; (b) K. S. Liddle and C. Parkin, *J. Chem. Soc., Chem. Commun.*, 1972, 26; (c) P. W. J. deGraaf, J. Boersma and G. J. M. Van der Kerk, *J. Organomet. Chem.*, 1976, **105**, 399–406; (d) K. A. Porter, A. Schier and H. Schmidbaur, *Organometallics*, 2003, **22**, 4922–4927.
- For seminal contributions on Au(I)/Au(III) manifolds, see: (a) A. S. K. Hashmi, T. D. Ramamurthi and F. Rominger, *J. Organomet. Chem.*, 2009, **694**, 592–597; (b) L. Cui, G. Zhang and L. Zhang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3884–3887; (c) G. Zhang, Y. Peng, L. Cui and L. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 3112–3115; (d) A. Iglesias and K. Muñiz, *Chem.-Eur. J.*, 2009, **15**, 10563–10569; (e) M. N. Hopkinson, A. Tessier, A. Salisbury, G. T. Giuffredi, L. E. Combettes, A. D. Gee and V. Gouverneur, *Chem.-Eur. J.*, 2010, **16**, 4739–4744; (f) G. Zhang, L. Cui, Y. Wang and L. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 1474–1475; (g) W. E. Brenzovich, J.-F. Brazeau and F. D. Toste, *Org. Lett.*, 2010, **12**, 4728–4731; (h) L. T. Ball, M. Green, G. C. Lloyd-Jones and C. A. Russell, *Org. Lett.*, 2010, **12**, 4724–4727; (i) A. D. Melhado, W. E. Brenzovich, A. D. Lackner and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 8885–8887; (j) T. de Haro and C. Nevado, *Angew. Chem., Int. Ed.*, 2011, **50**, 906–910; (k) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *Science*, 2012, **337**, 1644–1648; (l) C. X. Cambeiro,



- N. Ahlsten and I. Larrosa, *J. Am. Chem. Soc.*, 2015, **137**, 15636–15639. For selected reviews on this specific topic see: (m) P. Garcia, M. Malacria, C. Aubert, V. Gandon and L. Fensterbank, *ChemCatChem*, 2010, **2**, 493–497; (n) H. A. Wegner and M. Auzias, *Angew. Chem., Int. Ed.*, 2011, **50**, 8236–8247; (o) M. Hopkinson, A. D. Gee and V. Gouverneur, *Chem.–Eur. J.*, 2011, **17**, 8248–8262; (p) T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910–1925; (q) T. de Haro and C. Nevado, *Synthesis*, 2011, **16**, 2530–2539; (r) C. Nevado and T. de Haro, in *New Strategies in Chemical Synthesis and Catalysis*, ed. B. Pignataro, Wiley-VCH, Weinheim, 2012, p. 247.
- 14 (a) E. Tkatchouk, N. P. Mankad, D. Benitez, W. A. Goddard III and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 14293–14300; (b) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard III and F. D. Toste, *Angew. Chem., Int. Ed.*, 2010, **49**, 5519–5922; (c) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *J. Am. Chem. Soc.*, 2014, **136**, 254–264; (d) J. Guenther, S. Mallet-Ladeira, L. Estevez, K. Miqueu, A. Amgoune and D. Bourissou, *J. Am. Chem. Soc.*, 2014, **136**, 1778–1781; (e) M. Joost, A. Zeineddine, L. Estevez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune and D. Bourissou, *J. Am. Chem. Soc.*, 2014, **136**, 14654–14657; (f) D. A. Rosca, J. A. Wright, D. L. Hughes and M. Bochmann, *Nat. Commun.*, 2013, **4**, 2167–2175; (g) D. A. Rosca, J. Fernández-Cestau, J. Morris, J. A. Wright and M. Bochmann, *Sci. Adv.*, 2015, **1**, e1500761; (h) T. J. A. Corrie, L. T. Ball, C. A. Russell and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2017, **139**, 245–254.
- 15 Additional control experiments, experimental procedures, and full characterization of new compounds can be found in the accompanying ESI†
- 16 (a) M. Hofer and C. Nevado, *Eur. J. Inorg. Chem.*, 2012, **9**, 1338–1341; (b) M. Hofer and C. Nevado, *Tetrahedron*, 2013, **69**, 5751–5757.
- 17 (a) A. S. K. Hashmi, I. Braun, M. Rudolph and F. Rominger, *Organometallics*, 2012, **31**, 644–661; (b) L. Ye, Y. Wang, D. H. Aue and L. Zhang, *J. Am. Chem. Soc.*, 2012, **134**, 31–34; (c) A. Simmoneau, F. Jaroschik, D. Lesage, M. Karanik, R. Guillot, M. Malacria, J.-C. Tabet, J.-P. Goddard, L. Fensterbank, V. Gandon and Y. Gimbert, *Chem. Sci.*, 2011, **2**, 2417–2422; (d) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wietek, M. Rudolf and F. Rominger, *Angew. Chem., Int. Ed.*, 2012, **51**, 4456–4469; (e) M. M. Hansmann, M. Rudolf, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2012, **52**, 2593–2598.
- 18 For a Au-catalyzed oxidative homocoupling of alkynes using Selectfluor, see: A. Leyva-Pérez, A. Doménech, S. I. Al-Resayes and A. Corma, *ACS Catal.*, 2012, **2**, 121–126. The authors propose the transmetalation between two alkynyl-Au species in different oxidation states (Au(I)/Au(III)) as the key step for the formation of the new Csp–Csp bond.
- 19 For an Au-catalyzed heterocoupling of alkynes, see: H. Peng, Y. Xi, N. Ronaghi, B. Dong, N. G. Akhmedov and X. Shi, *J. Am. Chem. Soc.*, 2014, **136**, 13174–13177. The gold activation of the triple bond on an alkynyl-Au(III) intermediate is proposed as the key step for this transformation. Control experiments in our system ruled out the π -activation of complex **8** under the standard reaction conditions.
- 20 Ph_3PAuCl , which is observed in minimal quantities, is produced by the slow activation of the chlorinated solvent as demonstrated by additional control experiments (see Fig. S16–S19 in the ESI†).
- 21 B. B. Snider, D. M. Roush, D. J. Rodini, D. Gonzalez and D. Spindell, *J. Org. Chem.*, 1980, **45**, 2773–2785.
- 22 M. Hofer, A. Genoux, R. Kumar and C. Nevado, *Angew. Chem., Int. Ed.*, 2017, **56**, 1021.
- 23 W. J. Wolf, M. S. Winston and F. D. Toste, *Nat. Chem.*, 2014, **6**, 159–164.
- 24 The homocoupling production of methyl propiolate **18** presents a characteristic signal at 3.81 ppm in the ^1H NMR: J. A. Varela, L. Castedo, M. Maestro, J. Mahía and C. Saá, *Chem.–Eur. J.*, 2001, **7**, 5203–5213.
- 25 The reactivity observed for complex **10** could also be reproduced with its pentafluorophenyl analogue $\text{Ph}_3\text{PAu}(\text{C}_6\text{F}_5)(\text{Cl})_2$. See ref. 16.
- 26 (a) A. Maleckis, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2013, **135**, 6618–6621; (b) K. J. Stowers and M. S. Sanford, *Org. Lett.*, 2009, **11**, 4584–4587; (c) D.-A. Rosca, D. A. Smith and M. Bochmann, *Chem. Commun.*, 2012, **48**, 7247–7249.
- 27 D.-H. Zhang, L.-Z. Dai and M. Shi, *Eur. J. Org. Chem.*, 2010, **28**, 5454–5459.
- 28 J. G. Sharefkin and H. Saltzman, *Org. Synth.*, 1963, **43**, 62.
- 29 AcOH reacts with the NaHCO_3 present in the reaction media to form NaOAc thus bringing the effective energy of INT_2 to an even lower level.
- 30 (a) J. Vicente, M. D. Bermudez, J. Escribano, M. P. Carrillo and P. G. Jones, *J. Chem. Soc., Dalton Trans.*, 1990, 3083–3089; (b) J. Vicente, M. D. Bermudez and J. Escribano, *Organometallics*, 1991, **10**, 3380–3384; (c) T. Lauterbach, M. Livendahl, A. Rosellon, P. Espinet and A. M. Echavarren, *Org. Lett.*, 2010, **12**, 3006–3009; (d) M. Hofer, E. Gomez-Bengoa and C. Nevado, *Organometallics*, 2014, **33**, 1328–1332.
- 31 O. Schuster and H. Schmidbaur, *Organometallics*, 2005, **24**, 2289–2296.
- 32 Products of propiolate polymerization, which have been observed in the presence of gold nanoparticles (A. Leyva-Perez, J. Oliver-Meseguer, J. R. Cabrero-Antonino, P. S. Rubio-Marques, S. I. Al-Resayes and A. Corma, *ACS Catal.*, 2013, **3**, 1865–1873) were not detected in the reaction mixtures.
- 33 (a) T. J. Harrison, J. A. Kozak, M. Corbella-Pané and G. R. Dake, *J. Org. Chem.*, 2006, **71**, 4525–4529; (b) G. H. Woehrle, L. O. Brown and J. E. Hutchison, *J. Am. Chem. Soc.*, 2005, **127**, 2172–2183; (c) A. Zhdanko, M. Ströbele and M. E. Maier, *Chem.–Eur. J.*, 2012, **18**, 14732–14744; (d) M. Kumar, J. Jasinski, G. B. Hammond and B. Xu, *Chem.–Eur. J.*, 2014, **20**, 3113–3119.

